

ARCHIVES OF DISEASE IN CHILDHOOD

The Journal of the British Paediatric Association

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Cerebral blood flow velocity changes after rapid administration of surfactant

F Cowan, A Whitelaw, D Wertheim, M Silverman

Abstract

A computer linked Doppler system was used to make continuous measurements of cerebral blood flow velocity (CBFV) from the middle cerebral artery, mean arterial blood pressure (MAP) from the umbilical artery, and heart rate before, during, and for 20 minutes after the endotracheal administration of 200 mg/kg of porcine surfactant in 10 preterm infants with respiratory distress syndrome.

Within two minutes of surfactant administration, there was a median fall of 6 mm Hg (15%) fall in MAP and 36% in CBFV. There was a change in the Doppler spectra with almost complete loss of diastolic velocities. A rapid reduction in pulmonary vascular resistance with consequent left to right ductal shunting is one possible cause. These acute changes in MAP and CBFV after bolus surfactant administration may increase the risk of intraventricular haemorrhage.

There is evidence that surfactant replacement therapy can reduce mortality and pulmonary complications in preterm infants with respiratory distress syndrome.¹ However, Horbar *et al* reported a large multicentre randomised trial with a significantly increased number of severe periventricular haemorrhages among infants receiving bolus surfactant compared with control infants.² The Collaborative European Multicentre Study of Curosurf (porcine surfactant) found a surprisingly high incidence (26%) of severe intraventricular haemorrhage despite a big reduction in mortality and bronchopulmonary dysplasia among surfactant treated infants.¹ Other randomised trials have found a reduction in intraventricular haemorrhage among surfactant treated infants.^{3,4}

The bolus administration of surfactant into the trachea disturbs ventilation and could theoretically cause acute changes in pulmonary compliance, blood gases, pulmonary vascular resistance, blood pressure, and heart rate. Such changes, together with possible shunting through the ductus arteriosus, could have major effects on the cerebral circulation. Previous studies of the physiological changes during and after surfactant have attempted to examine these questions. All have found a rapid improvement in arterial oxygen tension (PaO₂). Halliday *et al* found evidence for increased pulmonary compliance but no increase in pulmonary blood flow.⁵ The same group used intermittent (every 15 minutes) Doppler measurements of peak flow velocity averaged over 10-15 cardiac cycles.⁶ There was no significant difference

between surfactant treated infants and controls in cerebral blood velocities measured on the internal carotid or pericallosal arteries. Jorch *et al* examined the effect of prophylactic natural surfactant on cerebral blood velocity in the internal carotid artery.⁷ These measurements were made at intervals of 10 minutes before and after surfactant treatment. There was no significant trend overall in cerebral blood velocity, arterial pressure, or carbon dioxide tension (PCO₂) when the surfactant treated infants were compared to control infants.

Heldt *et al* examined circulatory changes after human surfactant treatment using ultrasound Doppler colour flow mapping in a blind randomised study.⁸ The ductus arteriosus was patent in all the infants at entry to the study but left to right shunting was more common in the surfactant treated group. They concluded that surfactant reduced pulmonary vascular resistance, thereby facilitating shunting but had no intrinsic effect on ductal closure.

In the light of these uncertainties about an increased incidence of severe intraventricular haemorrhage and possible adverse effects on the preterm cerebral circulation of rapidly changing blood gases, blood pressure, and ductal shunting, we have carried out a study of the acute physiological changes during and after surfactant therapy using continuous measurement of cerebral blood flow velocity (CBFV), mean arterial pressure (MAP), heart rate, and blood gas tensions.

Patients and methods

Ten preterm infants with a clinical and radiological diagnosis of respiratory distress syndrome were studied. They were all being mechanically ventilated with an inspired oxygen concentration of 60% or greater and were paralysed with pancuronium and sedated with pethidine. Their median birth weight was 935 g (range 712-1660). Their median gestational age was 27.5 weeks (range 26-30 weeks). In all cases the parents gave informed consent to surfactant administration and the physiological measurements, and the protocol had been approved by the research ethics committee of the Hammersmith and Queen Charlotte's Special Health Authority. Median age at surfactant administration was 11.5 hours with a range of 7 to 72 hours.

Curosurf, a porcine natural surfactant (Chiesi Farmaceutici), was given in a total dose of 200 mg/kg (2.5 ml/kg) divided into two, by bolus injection through a 5 French gauge feeding catheter inserted down the endotracheal tube, which was temporarily disconnected from the ventilator. In the first six infants the first half

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dose was given with the head turned to the left side so that the catheter would tend to go down the right main bronchus. The ventilator was reconnected and when the infant had stabilised after about 30 seconds, the second half dose was given with the head turned to the right side, so that the catheter would tend to go down the left main bronchus.⁹ This head turning procedure necessitated a break in the CBFV measurements for about 15 seconds. The last four infants received surfactant with the head being held still in the midline so that CBFV measurements could be made continuously during instillation. One infant received surfactant 200 mg/kg on two separate occasions because of relapse after the first dose. Physiological measurements were thus made on 11 surfactant treatments.

In order to examine the effect of procedure independently of surfactant, measurements were made in one infant during disconnection from the ventilator and instillation of 2.5 ml/kg of 0.9% sodium chloride (saline) solution. This infant subsequently received surfactant. Saline administration was not studied in subsequent infants because of concern about a deterioration in their already critical condition.

Physiological measurement techniques

CBFV was measured using the duplex Doppler Vingmed CFM 700 system (Vingmed Sound A/S, Horten, Norway). Recordings were taken from the middle cerebral artery insonated via the temporal window. The position of the artery was first visualised using the imaging system and then blood velocities measured at an angle as close to zero as possible and at a measured depth. Thereafter, measurements were always made at the same angle and depth. An angle of zero was assumed for the calculation of intensity weighted mean velocity per consecutive heart beat. An electrocardiogram (ECG) recorded the heart rate.

The CFM 700, using a spectrum based velocity estimator, calculated the mean of the spectrum as the 50th percentile of the total spectral power each 10 milliseconds. The CFM 700 was interfaced to an Apricot XI computer (ACT Computers, Birmingham, England) which ran the Blood Velocity Analysis Program (Andiamo A/S, Oslo, Norway).¹⁰ This system calculated and stored on-line the time averaged velocities for each cardiac cycle (CBFV) together with heart rate and MAP.

MAP was measured continuously via an umbilical artery catheter, pressure transducer (Medex) and monitor (Tektronix). The pressure transducer's zero reading was checked at the start of each study. Arterial blood velocity spectra, arterial pressure waveform, and ECG were all stored on videotape.

We made a continuous recording of blood velocity, arterial pressure, and heart rate during a stable period before the bolus injection, during the surfactant administration, and intermittently up to 20 minutes afterwards. Pourcelot's resistance index (PI) was calculated:

$$PI = \frac{\text{peak systolic velocity} - \text{end diastolic velocity}}{\text{peak systolic velocity}}$$

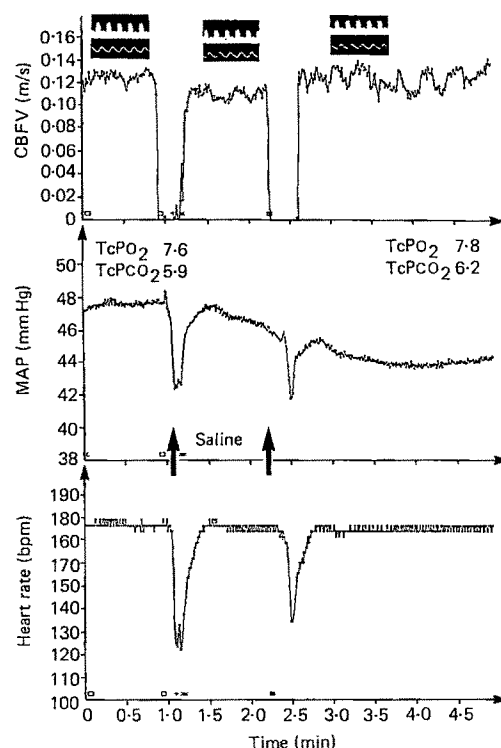


Figure 1 Simultaneous recording of middle cerebral artery CBFV, MAP, and heart rate over a five minute period. The arrows indicate the timing of endotracheal administration of 2×1.25 ml/kg 0.9% sodium chloride (saline) in a preterm infant with respiratory distress syndrome. Representative Doppler spectra are shown (inserts) with no change in the diastolic velocities.

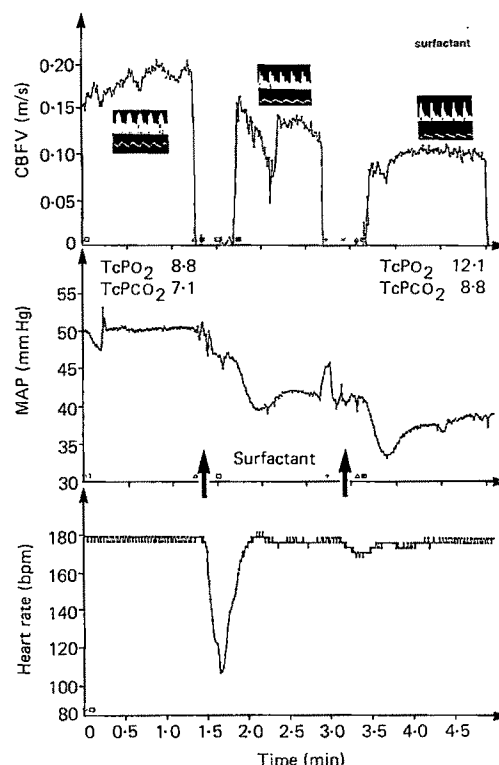


Figure 2 Simultaneous recording of CBFV, MAP, and heart rate over a five minute period. The arrows indicate the timing of endotracheal administration of 2×1.25 ml/kg surfactant in a preterm infant with respiratory distress syndrome. Representative Doppler spectra are shown (inserts) with a large drop in the diastolic velocities.

Transcutaneous PO_2 and PCO_2 were measured using a TCM3 system (Radiometer) to follow trends but direct arterial blood gas measurements before and five, 10, and 20 minutes after surfactant administration were used to assess the effects of surfactant. Statistical comparisons of data used the paired Student's t test where the distributions were Gaussian and the Wilcoxon signed rank test where the distributions were non-Gaussian.

Results

INDIVIDUAL RECORDINGS

During disconnection and instillation of saline in one infant (fig 1), there was an acute 4 to 5 mm Hg (10%) fall in MAP, eventually settling 3 mm Hg (7%) below the starting value, and a brief 40 to 50 beats/minute (bpm) fall in heart rate. The CBFV, although showing variability, was unchanged after the saline. The velocity spectrum of CBFV was unchanged by disconnection and saline administration, with no loss of diastolic velocity.

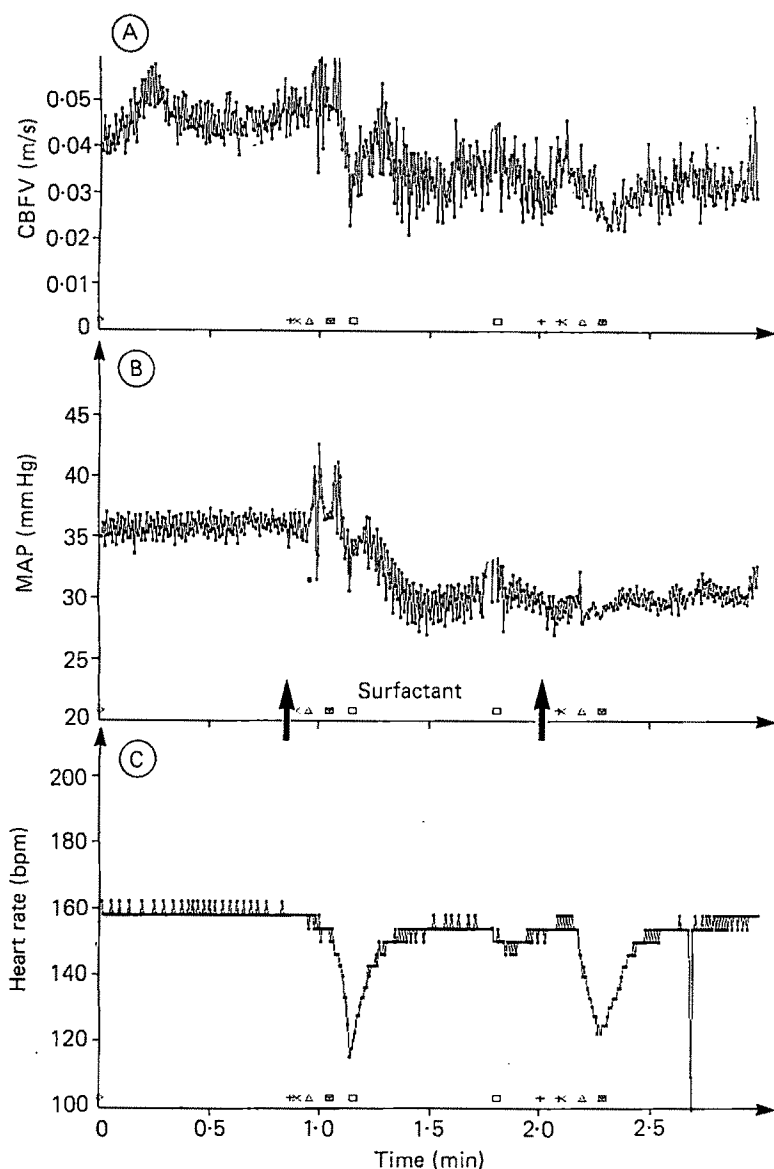


Figure 3 Continuous recording of middle cerebral artery CBFV, MAP, and heart rate during administration of 2×1.25 ml surfactant (timing indicated by the arrow).

In the same infant there was a drop in heart rate at the first dose of surfactant but not at the second surfactant treatment (fig 2). MAP fell from 50 mm Hg to about 40 mm Hg after the first dose and then fell to about 35 mm Hg after the second dose. This fall in MAP (greater than 20%) was much greater than that seen after saline and persisted for at least 20 minutes. CBFV fell from 0.18 m/sec and remained at 0.1 m/sec (44% fall). The velocity spectrum shows a complete change of shape with a huge reduction in diastolic velocities. Figures 1 and 2 show the administration of saline and surfactant respectively with head turning necessitating two gaps in the velocity recordings.

Figure 3 shows a continuous recording made during surfactant administration with the head held steady in the midline with the infant supine. There were two brief bradycardias while the endotracheal tube was disconnected. The falls in MAP (about 15%) and CBFV (nearly 40%) persisted until the end of the recording.

POOLED MEASUREMENTS

Median initial change in MAP during all 11 surfactant administrations was -6 mm Hg with a range of $+2$ to -17 mm Hg, only one infant showing a small initial rise in MAP (fig 4A). Before surfactant administration, MAP had a mean (SD) of 38.1 (6.9) mm Hg. At two minutes mean MAP was 31.4 (3.9) mm Hg, by five minutes 33.6 (3.2) mm Hg, and at 10 minutes 34.1 mm Hg. MAP was still reduced 20 minutes after administration in nine cases, with a median change of -5 mm Hg and a range of $+6$ to -10 mm Hg. Mean values for MAP at two, five, 10, and 20 minutes were all significantly lower than the presurfactant value ($p < 0.01$ in all cases). Mean change in heart rate was -35 with a range of $+5$ to -102 bpm, but these changes were transient and resolved within five minutes (fig 4B).

There was a substantial initial reduction in CBFV in nine of the 11 cases (median change -36% , range $+11\%$ to -55%) (fig 5A). Median CBFV before surfactant was 0.056 m/sec (range 0.03 – 0.184). During surfactant administration, median CBFV fell to 0.035 m/sec (range 0.03 – 0.084) and at five minutes the median was 0.042 m/sec (range 0.02 – 0.1). These values for CBFV were significantly lower than the presurfactant values ($p < 0.01$ in both cases). CBFV values at 20 minutes, median 0.048 m/sec (range 0.03 – 0.11) were not significantly different from the presurfactant values ($p = 0.16$) but there was still considerable scatter in individual cases, median change from the presurfactant value being -24% with a range of $+44\%$ to -39% . Three infants had CBFV values at 20 minutes that were higher than those before surfactant.

Peak systolic velocity in the middle cerebral artery was maintained during surfactant administration but there was a reduction to zero in end diastolic velocity in seven of the 11 cases by two minutes and 10 of the 11 by five minutes (fig 5B). This is the type of change shown in an individual infant in figure 2. Two of the infants had zero end diastolic velocity before surfactant administration and this persisted. Diastolic

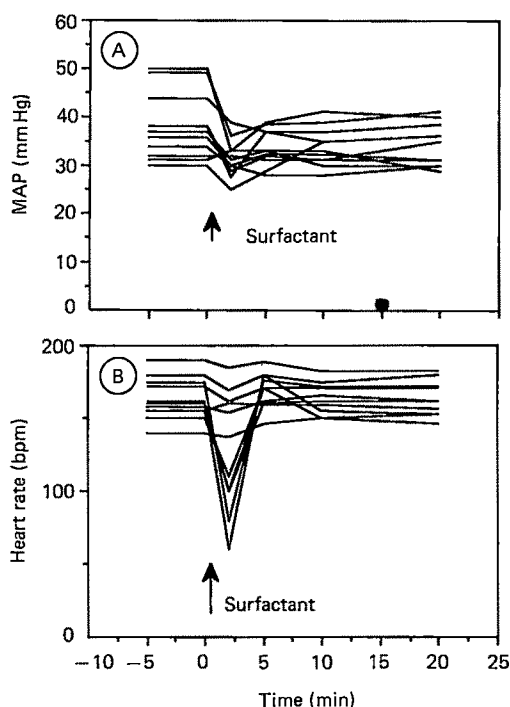


Figure 4 MAP and heart rate from all 11 surfactant treatments: (A) shows, a significant and sustained drop in MAP and (B) only a transient decrease in heart rate.

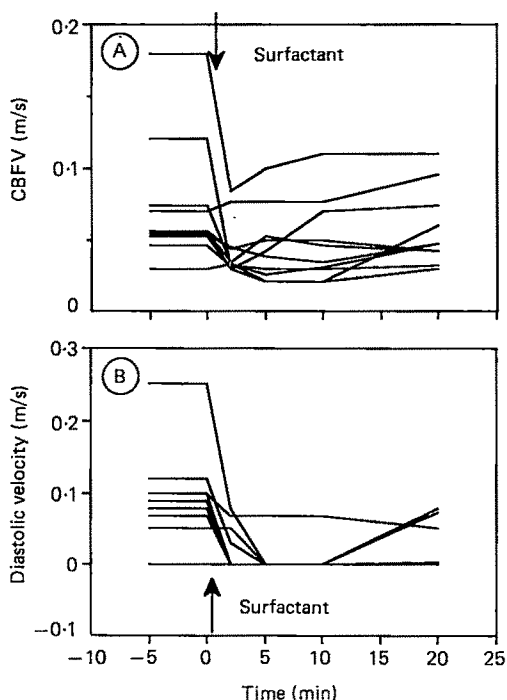


Figure 5 (A) Middle cerebral artery CBFV from all 11 surfactant treatments. There was a significant reduction during surfactant administration and at five minutes. (B) Diastolic velocities from the middle cerebral artery of all 11 surfactant treatments. In two cases the diastolic velocity was 0 even before surfactant treatment.

velocities at two and five minutes were significantly different from presurfactant values ($p < 0.01$ in both cases). By 20 minutes, four of the infants had positive diastolic velocities (fig 5B). Pourcelot's resistance index rose from a

median of 0.68 before surfactant to a median of 1.0 ($p < 0.01$ at two and five minutes).

Arterial P_{O_2} showed a rapid increase from a mean (SD) of 7.5 kPa to a mean (SD) of 13.7 (4.8) kPa five minutes after surfactant ($p = 0.002$). After this time the inspired oxygen concentration was reduced to prevent hyperoxia. P_{CO_2} rose from a mean (SD) of 5.15 (0.80) kPa to a mean (SD) of 5.39 (0.89) kPa five minutes after surfactant ($p < 0.05$). By 10 and 20 minutes mean P_{CO_2} had returned to baseline value without a change in the ventilator settings.

Discussion

Using continuous recording of CBFV before, during, and after surfactant administration, this study showed a significant fall in velocities, and, by inference, cerebral blood flow, immediately after and for five minutes after surfactant treatment. By 20 minutes CBFV had returned to baseline levels in some cases. Simultaneous recording of MAP via an indwelling arterial catheter showed a significant fall persisting to 20 minutes. Heart rate fell transiently but recovered quickly.

The persistent though modest reduction in MAP might have been due to increased transmission of high airway pressure to the circulation, thus impeding venous return. Alternatively, the drop in MAP could be an effect of a widened pulse pressure resulting from left to right ductal shunting (see below) or a direct pharmacological effect of surfactant. We have noticed some flushing after porcine surfactant suggesting a peripheral vasodilator effect of one of its constituents. Whatever the cause, a considerable drop in MAP is undesirable as early hypotension has been shown to be a risk factor for intraventricular haemorrhage.¹¹

The fall in mean CBFV could be explained by the immediate drop in MAP and by the fall in end diastolic velocity with maintenance of peak systolic velocity (fig 5B). Before treatment with surfactant all the infants had two resting recordings of CBFV and MAP to determine whether CBFV varied with changes in MAP or not. In two infants no spontaneous alterations in MAP occurred during these recordings and hence it was not possible to draw any conclusions. In the other eight infants only one showed any ability to maintain a stable CBFV in the face of changing MAP. Thus seven of the eight infants in whom it was possible to make a judgment probably had poor or absent cerebral autoregulation as one might expect at this range of gestational age¹² and one would expect changes in MAP to be reflected in CBFV.

The striking loss of diastolic velocities is consistent with a sudden reduction in pulmonary artery pressure allowing left to right shunting through the patent ductus arteriosus and a cerebral steal phenomenon.¹³ Whether sudden changes to ductal shunting or cerebral steal can increase the risk of intraventricular haemorrhage is not known. It could be suggested that surfactant increases lung compliance and so allows the high airway pressure to exert its effect on the circulation. However, the rapidity and short duration of the CBFV changes together with the failure of P_{CO_2} to decrease

would be against improvement in lung compliance being the major mechanism behind the changes we have observed.

Previous attempts at investigating the effect of surfactant on the cerebral circulation have used very brief (4–6 seconds) recordings every 10–15 minutes.^{6,7} Our continuous recordings around the time of surfactant therapy have shown that there are appreciable swings in CBFV, MAP, and heart rate which would probably have been missed with intermittent measurements. The noticeable changes in heart rate and MAP may be partly, but not entirely, explained by disconnection from the positive pressure oxygen and the rapid decrease in alveolar oxygen. The sheer volume of the endotracheal bolus (2.5 ml/kg) is likely to have a temporary obstructive effect and many infants did show a transient rise in PCO_2 . The manipulation involved in turning the head probably disturbs the infants, but this cannot be the major factor as the effects of an equivalent volume of saline (figs 1 and 2) were minor compared with the instillation of surfactant.

Most infants had a small and transient rise in PCO_2 after surfactant and also an appreciable and persistent rise in PO_2 . Increasing PCO_2 is usually, but not always, associated with a rise in CBFV.^{14,15} Hyperoxia has been found to have extremely small effect in reducing CBFV, and the rise in PO_2 after surfactant could not have produced the large fall in CBFV found.¹⁶

In view of the considerable increase in intraventricular haemorrhage reported by Horbar *et al* and the association between hypotension¹¹ and fluctuations in CBFV¹⁷ and haemorrhage, it could be that the acute changes in the cerebral circulation related to surfactant administration might increase the risk of intraventricular haemorrhage. The effects on the systemic and cerebral circulation might be reduced by slower continuous infusion of surfactant without physical disturbance to the infant and the use of an endotracheal connector with a side arm for the infusion to avoid disconnection, bolus injection, and interruption of ventilation.

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Hypocapnia and cerebral ischaemia in hypotensive newborn piglets

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Abstract

This study tested the hypothesis that hypocapnia superimposed upon hypotension produces a further reduction in cerebral blood flow velocity (CBFV). In 12 newborn piglets, CBFV was measured continuously by Doppler ultrasound through an artificial fontanelle. Hypotension was induced by removing 30 ml/kg of blood. Increasing the ventilator rate reduced the average arterial carbon dioxide tension from 5.5 to 2.0 kPa. When mean arterial pressure (MAP) was held steady at 45 mm Hg or above, hypocapnia produced a substantial drop in CBFV but, in all the piglets with MAP below 38 mm Hg, hypocapnia failed to change CBFV by 10%. Hypocapnia produced an increase in lactate in sagittal sinus blood but cerebral venous hypoxanthine concentrations were not affected by hypocapnia. Hyperventilation (without haemorrhage) produced a significant drop in MAP, preventable by infusing colloid.

Hypocapnia itself does not further reduce CBFV in the hypotensive piglet. However, the pressure effect of hyperventilation may significantly impair the cerebral circulation.

Despite the great improvements in the survival of premature infants, there are reports of increasing numbers of handicapped survivors with cerebral palsy.^{1,2} The most important neuropathological lesion associated with spastic diplegia in premature infants is periventricular leucomalacia. This is a bilateral cerebral lesion in the white matter furthest from the arterial blood supply. The aetiology is not fully understood and no treatment has been shown to be effective in preventing periventricular leucomalacia. On theoretical grounds, it is likely that hypotension is an important causative factor but the occurrence of periventricular leucomalacia is not consistently associated with hypotension.³ There must be other aetiological factors.

It has been proposed that a very low arterial carbon dioxide tension (P_{aCO_2}) (hypocapnia) may be important in the aetiology of ischaemic brain damage in newborns.⁴ When blood pressure is normal, raising P_{aCO_2} increases cerebral blood flow and decreasing P_{aCO_2} decreases cerebral blood flow. When blood pressure falls, the brain tries to maintain blood flow by progressively vasodilating and eventually becomes maximally vasodilated. If hypocapnia caused cerebral vasoconstriction in this situation, cerebral blood flow could be reduced to a critically low level with ischaemic damage

following. Although brain lesions have not been demonstrated in experimental animals after hypocapnia,⁵ slowing of the electroencephalogram has been noted in adult humans during hyperventilation. These changes could be reversed by hyperventilating with 100% oxygen.⁶ The normal escape mechanisms that inhibit excessive vasoconstriction may not operate in the immature neonatal cerebral circulation.

Inadvertent hypocapnia may occur when premature infants are mechanically ventilated for transport by ambulance or helicopter from the place of birth to the neonatal intensive care unit as infants do not usually have any form of carbon dioxide monitoring during transport. Hypocapnia may occur any time that an infant is mechanically ventilated without careful monitoring of P_{aCO_2} , for example during surgical anaesthesia. This is particularly likely with infants who do not have respiratory distress syndrome and stiff lungs.

Calvert *et al* reported a case-control study of 15 infants with periventricular leucomalacia.⁷ The infants with periventricular leucomalacia had experienced significantly lower P_{aCO_2} values during the first 72 hours than had the control infants. The length of time that P_{aCO_2} was below 3.3 kPa was longer in the infants who subsequently developed periventricular leucomalacia. Calvert *et al* had no data on blood pressure but discussed the likelihood that the infants with periventricular leucomalacia had suffered hypotension as well as hypocapnia. Evidence for the involvement of hypocapnia and hypoperfusion in the aetiology of neurological deficit after cardiopulmonary bypass in adult patients has also been reported.⁸

In this study we tested the hypothesis that hypocapnia superimposed upon hypotension in the newborn can further reduce cerebral blood flow velocity and thereby increase the risk of cerebral ischaemia. None of the previous papers on hypocapnia, hypotension, and cerebral blood flow have dealt with newborns and the study would be unethical in human infants. The newborn piglet was chosen as the experimental model because of the great similarities in cardiovascular and respiratory systems, cerebral circulation, and body size between the piglet and human infant.

Methods

The experiments were performed on 12 newborn piglets aged from 12 hours to 3.5 days and weighing 1.1 to 2.8 kg, which were kept with the sow until three hours before the

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experiment started. Venous access was secured during brief ether anaesthesia. An initial dose of 50 mg/kg of chloralose and 250 mg/kg urethane was given during 15 minutes and followed by a continuous infusion of 12.5 mg/kg/hour chloralose and 62 mg/kg/hour of urethane throughout the experiment. Maintenance fluid as 5% dextrose was given at 7.5 ml/kg/hour. A rectal temperature of 39°C was maintained by a heating pad and overhead heater.

A tracheostomy was performed and each piglet was paralysed with pancuronium 0.2 mg/kg intravenously and mechanically ventilated with 25–30% oxygen during surgery, care being taken to avoid any hypoxaemia. Both umbilical arteries and the umbilical vein were catheterised in piglets less than 48 hours old. In slightly older piglets a femoral artery and subclavian vein were catheterised. These catheters were used for blood sampling, continuous arterial pressure recording, and infusion of fluids and drugs. In five animals a catheter was inserted into the right internal jugular vein with the tip just below the brain and in two animals a catheter was inserted into the sagittal sinus. These catheters were used for hypoxanthine and lactate blood sampling. Blood samples were separated within one minute and plasma kept frozen until hypoxanthine was measured by high precision liquid chromatography.⁹ Plasma lactate was measured by standard laboratory techniques. In order to measure intracerebral blood velocities with Doppler ultrasound, an artificial fontanelle of 1 cm diameter was made just lateral to the midline where the cranial sutures meet.

All values are given as median values with the 95% confidence interval¹⁰ and are listed in the table. Comparisons of grouped data were made using the Wilcoxon signed rank test.¹⁰

The experimental protocol was as follows:

HYPOCAPNIA DURING NORMOTENSION

Median mean arterial pressure (MAP) at the start of the protocol was 48 mm Hg (37 to 75). After recording cerebral blood flow velocity (CBFV) and MAP continuously for five minutes with a normal PaCO_2 (5.5 kPa), hyperventilation was produced by increasing the frequency of the ventilator from 20 (inspiratory time 0.3 seconds, expiratory time 2.7 seconds) to 100 breaths/minute (bpm) (inspiratory time 0.3 seconds, expiratory time 0.3 seconds). This produced a rapid fall in PaCO_2 within 10 minutes to 2.0 kPa. Three animals received 20 ml/kg 5% albumin during hyperventilation to correct the tendency for MAP to fall. CBFV recording was continued while hyperventilation was continued for a further 10 minutes and then normal ventilation was resumed (18 to 20 bpm). The PaCO_2 rose back to the normal range.

HYPOCAPNIA DURING HAEMORRHAGIC

HYPOTENSION

With the PaCO_2 at 5.4 kPa, blood was withdrawn through a catheter into heparinised syringes at a rate of 1–2 ml/kg/minute until 30 ml/kg had been removed. This produced a median fall in

MAP of 37% to 32 mm Hg as well as a median fall of 35% in CBFV.

HYPOTENSIVE HYPOCAPNIA

In a stable hypotensive condition, at least 30 minutes after the end of the bleed, baseline recordings with a normal PaCO_2 were obtained. Hyperventilation was again produced by ventilating at 100 bpm. The PaCO_2 fell from 5.5 kPa to 1.9 kPa. Blood was transfused back into the piglet during hyperventilation at a rate sufficient to hold the MAP steady. Hyperventilation and recording of CBFV and MAP continued. After 20 minutes of hyperventilation the last blood samples were obtained and the experiment was terminated by rapid injection of potassium chloride.

CBFV RECORDINGS

As long as the cross sectional area of the vessel recorded from is constant, changes in blood velocity are proportional to changes in blood flow.¹¹ A 10 MHz Doppler ultrasound system (SD 100 Vingmed Sound) was used. By adjusting the depth of the sample volume and direction of insonication through the artificial fontanelle, precise localisation on an intracerebral artery could be achieved. In each piglet, the same artery (1.7 cm deep and 1.5 cm lateral to the midline) was used for recording at a constant angle with the transducer held in place manually. The Doppler system was interfaced to an Apricot XI computer. Every 5 ms the computer was fed the mean CBFV calculated from the Doppler spectrum, MAP, and heart rate. CBFV, MAP, and heart rate were all displayed in real time on a screen during the whole experimental period and stored on disc.

Results

HYPOCAPNIA DURING NORMOTENSION

Hyperventilating the piglets by increasing the ventilator rate from 20 to 100 bpm produced an appreciable drop in MAP. This is shown in the table and illustrated in fig 1. MAP in nine piglets fell from a median of 48 mm Hg (37–75) to a median of 36 mm Hg (29–56) and in three piglets where albumin was given, MAP fell from a median of 46 to 41 mm Hg. Thus during hyperventilation the median MAP of all 12 piglets was 41 mm Hg (33 to 51). In all the piglets with a MAP above 44 mm Hg there was a definite fall in cerebral blood flow velocity during hyperventilation. These young piglets nearly all showed a proportional decrease in CBFV with MAP. Hence when calculating the effect of low PaCO_2 on CBFV, the effect of blood pressure change has to be corrected for. This is illustrated in fig 1 where CBFV fell by nearly 50% whereas MAP fell by less than 25% during hyperventilation. Thus 25% was subtracted from the initial CBFV to calculate the starting value from which the change during hypocapnia was calculated. The table shows the CBFV fell by a median of 20% (10–33) during this normotensive hypocapnia. A cerebrovascular response to hypocapnia was considered to be present if CBFV fell by at least 10%.

Cardiovascular changes during experiment. Values are medians (95% confidence intervals)

	Normotensive hypocapnia		Haemorrhagic hypotension		Hypotensive hypocapnia	
	Before	During	Before	During	Before	During
MAP (mmHg):						
(n=9)	48 (47 to 75)	36 (29 to 56)				
(n=3, albumin)	46 (45 to 55)	41 (40 to 51)				
(n=12)	48 (46 to 68)	41 (33 to 51)	51 (46 to 56)	32 (25 to 37)	27 (24 to 38)	27 (24 to 38)
Heart rate (bpm)*	178 (167 to 198)	195 (180 to 210)	190 (165 to 220)	225 (170 to 310)	240 (170 to 310)	243 (185 to 280)
PaO ₂ (kPa)*	14.6 (12.8 to 17.0)	13.9 (11.7 to 16.0)	14.0 (12.4 to 16.7)	14.2 (11.8 to 15.7)	14.6 (12.1 to 17.1)	13.8 (10.4 to 15.9)
PaCO ₂ (kPa)*	5.5 (5.0 to 6.0)	2.0 (1.7 to 2.4)	5.4 (5.1 to 6.0)	5.4 (4.7 to 6.0)	5.5 (5.3 to 6.4)	1.9 (1.6 to 2.1)
pH*	7.36 (7.32 to 7.40)	7.70 (7.65 to 7.76)	7.35 (7.35 to 7.41)	7.32 (7.28 to 7.44)	7.29 (7.25 to 7.43)	7.63 (7.50 to 7.70)
Base excess (mmol/l)*	-2.7 (-4.1 to -0.9)	1.0 (-0.9 to 5.1)	-2.1 (-5.1 to 0.0)	-3.2 (-5.8 to 0.3)	-3.2 (-8.5 to 1.0)	-2.5 (-10 to 0.1)
% Reduction in CBFV*		20.0 (10.0 to 33.0)		34.5 (17.0 to 41.0)		0.0 (0.0 to 6.0)

*n=12.

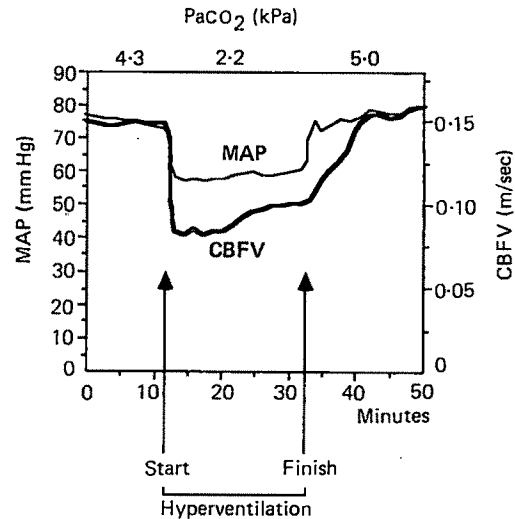


Figure 1 Continuous recording of CBFV and MAP in a piglet during hyperventilation with normal blood pressure. There is a fall in MAP but a much larger fall in CBFV indicating a cerebrovascular response to hypocapnia.

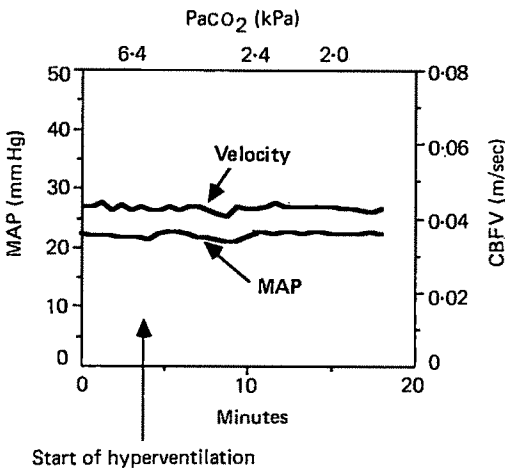


Figure 2 Continuous recording of CBFV and MAP in a piglet during hyperventilation with hypotension after haemorrhage. Blood was transfused back to maintain a steady blood pressure during hyperventilation. There was no change in CBFV indicating an absent cerebrovascular response to hypocapnia.

HYPOCAPNIA DURING HAEMORRHAGIC HYPOTENSION

During hyperventilation after the haemorrhage, MAP was maintained by blood retransfusion. In eight out of nine piglets with MAP below 38 mm Hg, hypocapnia failed to produce any further fall in CBFV (fig 2), and the ninth piglet showed only a 6% fall. In one piglet with MAP

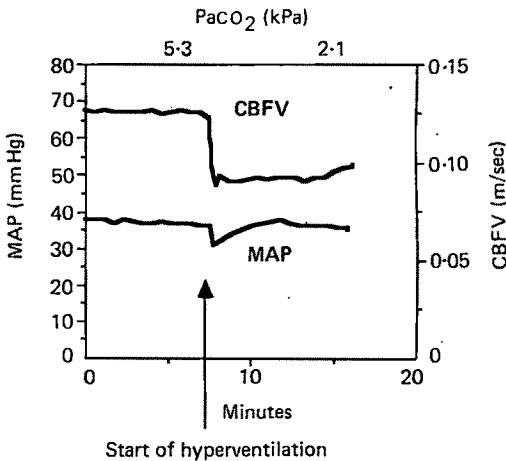


Figure 3 Continuous recording of CBFV and MAP during hyperventilation with MAP at 38 mm Hg after haemorrhage. Albumin was transfused to maintain blood pressure. There was a large fall in CBFV indicating a cerebrovascular response to hypocapnia.

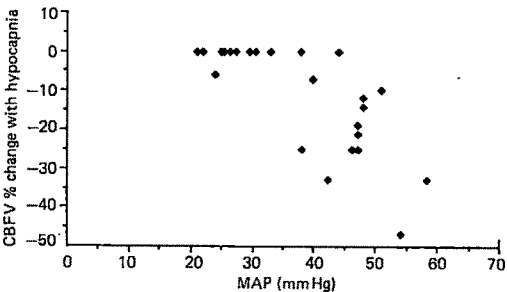


Figure 4 Percentage change in CBFV in 12 piglets each with two hypocapnia challenges at differing blood pressures, before and after haemorrhage.

38 mm Hg after haemorrhage, the normal cerebrovascular response to hypocapnia was preserved and this is illustrated in fig 3.

CEREBROVASCULAR RESPONSE TO HYPOCAPNIA AT DIFFERENT MAP

When all 24 hyperventilation challenges are considered together as in fig 4, it can be seen that the cerebrovascular response to hypocapnia was clearly present when the MAP was over 44 mm Hg. When MAP was below 38 mm Hg, CBFV responses were absent or less than 10%.

Figure 5 shows that jugular venous or sagittal sinus plasma hypoxanthine concentration showed no significant increase during either normotensive hypocapnia or hypotensive hypocapnia. In the seven animals examined there was an increase in plasma hypoxanthine as the

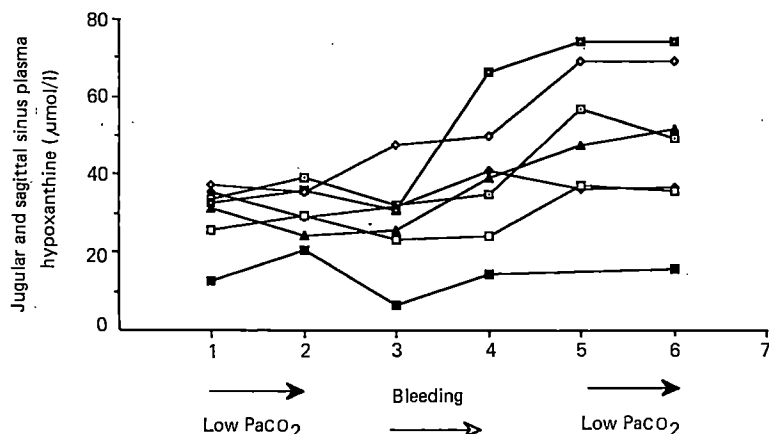


Figure 5 Serial plasma hypoxanthine concentrations in blood draining the brain, either from the jugular vein (five piglets) or from the sagittal sinus (two piglets). Numbers on X axis indicate samples before (1) and during (2) normotensive hypocapnia, before (3) and during (4) haemorrhagic hypotension and before (5) and during (6) hypotensive hypocapnia. There was no change in plasma hypoxanthine during either normotensive (2 v 1) or hypotensive (6 v 5) hypocapnia. There was a significant increase in hypoxanthine after the haemorrhage (5 v 3, $p \leq 0.005$).

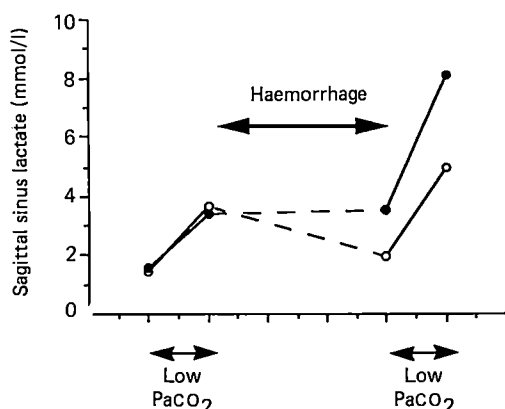


Figure 6 Plasma lactate concentration draining the brain via the sagittal sinus (two piglets). There was a definite increase in lactate during normotensive and hypotensive hypocapnia.

arterial pressure fell with blood loss. Figure 6 shows that sagittal sinus plasma lactate concentration increased during normotensive and hypotensive hypocapnia.

Discussion

When MAP was steady at a level below 38 mm Hg, hypocapnia produced negligible reduction in CBFV. This is clear evidence against our hypothesis that hypocapnia could further impair the cerebral circulation during hypotension. It would be an appropriate physiological response for the cerebral circulation to vasodilate in response to hypotension and to try to maintain the best possible cerebral circulation at all costs. Thus it seems that the cerebral vasodilator response to hypotension cannot be over-ridden by the cerebral vasoconstrictor response to hypocapnia. Hypoxanthine is probably the best available plasma marker of cellular hypoxia (or failure to make ATP)¹² and the lack of any significant increase in hypoxanthine in jugular or sagittal sinus blood is further evidence that hypocapnia does not, by itself, produce cerebral ischaemia.

The increase in lactate in sagittal sinus blood

is not necessarily evidence of cerebral ischaemia. There is much evidence that the increase in pH with hyperventilation changes the activity of glycolytic pathway enzymes and thus increases lactate production while cerebral levels of phosphocreatine, ATP, and energy charge remain unchanged.^{13 14} Mitchenfelder and Theye have demonstrated in dogs that hypocapnia can shift the oxygen-haemoglobin dissociation curve in sagittal sinus blood to the left (Bohr effect) thus reducing oxygen availability to the tissues.¹⁵ This was associated with a change towards anaerobic metabolism. Lactate has been postulated to have a role as a cerebral vasodilator but the rise in lactate during hypotensive hypocapnia was not accompanied by further vasodilatation (fig 2). This finding suggests that the cerebral circulation was already maximally vasodilated during hypotension.

Do our findings mean that overventilation is harmless? Not necessarily. The anecdotal observations of an association between hypocapnia and subsequent neurological impairment may be due, not to a direct effect of hypocapnia on the cerebral circulation, but to the pressure effect of hyperventilation on the circulation. We observed that hyperventilation produced a median drop in MAP of 12 mm Hg. A fall in blood pressure of such magnitude combined with the Bohr effect on oxygen-haemoglobin dissociation could certainly impair cerebral oxygenation in a critically ill infant. We have previously described how increases in ventilator pressure can reduce CBFV in newborn infants.¹⁶ If the infant's lungs are relatively compliant the ventilator pressure will be transmitted to the circulation thus producing a resistance to venous return to the right atrium, which would tend to reduce cardiac output. In addition, increased jugular venous pressure constitutes a resistance to cerebral blood flow.

In conclusion, the cerebral circulation of the hypotensive newborn piglet does not vasoconstrict in response to hypocapnia but positive pressure hyperventilation may significantly impair the cerebral circulation and oxygenation. Thus it would seem wise to avoid hypocapnia in mechanically ventilated infants particularly those with hypotension, hypovolaemia, or anaemia.

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Effects of intrauterine growth retardation on postnatal visceral and cerebral blood flow velocity

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Abstract

Blood flow velocity and pulsatility index were measured with Doppler ultrasound in the superior mesenteric artery, coeliac axis, and anterior cerebral artery in 18 very low birth weight, small for gestational age infants, and compared with findings from 18 weight matched, and 18 gestation matched, appropriate for gestational age controls. Mean velocity in the superior mesenteric artery was lower in the small for gestational age infants (15 cm/s) than in the gestation matched control group (20.4 cm/s). In those small for gestational age infants who had evidence of fetal hypoxia the mean velocity in the superior mesenteric artery was even lower (11.5 cm/s). There were no differences in velocity in the cerebral artery among the groups. Infants who were small for gestational age still had significantly lower superior mesenteric artery velocity than gestation matched controls at 1 week of age.

The results suggest a specific reduction in visceral perfusion in infants who are small for gestational age and who have experienced fetal hypoxia, and this could predispose these infants to necrotising enterocolitis.

Cordocentesis has shown that fetuses that are extremely small for gestational age are chronically hypoxaemic and acidotic.¹ It has also been shown by Doppler studies of the fetal circulation that in fetal hypoxaemia there is centralisation of flow with increased blood velocity and a decreased pulsatility index in the cerebral circulation, and decreased velocity with increased impedance in the aorta.² This response maintains cerebral oxygenation while organs that are supplied by the descending aorta are likely to be deprived. In fetuses that are more severely hypoxic there is complete absence of end diastolic frequencies in the descending aorta, and after birth these infants are at increased risk of developing necrotising enterocolitis and haemorrhage.³ This predisposition to necrotising enterocolitis could result from hypoxic-ischaemic tissue damage occurring in utero or from persisting abnormalities of perfusion after delivery.

To determine whether abnormalities of perfusion in the fetus persist into postnatal life, we have studied blood flow velocity in the superior mesenteric artery and the coeliac axis in a group of very low birthweight (VLBW) infants with intrauterine growth retardation (IUGR) detected before delivery. We have compared the results with those from weight matched and gestation

matched control groups of babies of appropriate birth weight for gestational age. To find out if our findings are specific to the splanchnic circulation we also measured blood flow velocity in the anterior cerebral artery.

Patients and methods

Doppler studies of the superior mesenteric artery, coeliac axis, and anterior cerebral artery were made on 18 infants admitted to our unit whose birth weight was less than 1500 g and who were less than the 10th centile for gestation. In all cases growth retardation was suspected antenatally, and on ultrasound examination the fetal abdominal circumference was less than the 5th centile for gestation. Antenatal Doppler studies indicating the presence or absence of end diastolic frequencies in the fetal aorta had been done as previously described.³ Because this hospital is a referral centre for antenatal diagnosis, the proportion of fetuses with absent end diastolic frequencies (12/18) was higher than would normally be expected. For each index case a weight matched and a gestation matched control infant was selected retrospectively from a pool of 70 appropriate for gestational age infants who needed intensive care and who also had Doppler measurements made. The matched cases were the infants with the closest weight or gestation to the index case, who also had Doppler data for the same days of age. For the three infants who were small for gestational age from multiple pregnancies, the appropriately grown co-twin or co-quadruplet was used as a gestation matched control (tables 1 and 2).

Measurements were made for each infant on days 1, 3, and 7, after delivery. Data were only included in the analysis if a measurement was available on the same day in both the index and control cases.

Blood flow velocity waveforms were obtained from each artery using a duplex ultrasound imaging and Doppler system (Hewlett Packard Sonos 100 with 7.5 MHz imaging and 5.0 MHz Doppler transducer). The artery was visualised using real time ultrasound, and the signals from a known segment of the artery were sampled by range gating. We corrected for the angle of insonation of the artery and eliminated artefact arising from movement of the vessel wall with a 100 Hz filter. The time averaged mean of the peak velocity envelope was calculated from four consecutive cardiac cycles by hand planimetry. The pulsatility index of the waveform was calculated with a Doptek 9000 spectrum analyser from signals recorded on videotape. (The pulsatility index is equal to the difference between

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Table 1 Comparability of the groups

	Small for gestational age infants (n=18)	Control infants	
		Weight matched (n=18)	Gestation matched (n=18)
Mean (range) birth weight (g)	845 (434-1380)	849 (506-1404)	1565 (882-2482)
Mean (range) gestation (weeks)	30.5 (25-34)	25.6 (23-28)	30.5 (26-34)
No of survivors	12	14	17

Table 2 Comparability at times of measurement between small for gestational age infants and their control groups. Figures are expressed as number of infants except where otherwise stated

	Small for gestational age (n=18)	Control infants	
		Weight matched (n=18)	Gestation matched (n=18)
Day 1 (n=18)*			
Mean (range) arterial oxygen tension (kPa)	8.6 (5.3-13.3)	9.0 (4.4-11.6)	8.8 (4.4-15.2)
Mean (range) arterial blood pressure (mmHg)	35.9 (24-53)	34.6 (22-52)	37.3 (30-58)
No receiving artificial ventilation	12	18	15
No with umbilical arterial catheter	11	17	15
Day 3 (n=10)			
No receiving artificial ventilation	5	8	5
No with umbilical arterial catheter	4	10	5
No receiving enteral feeds	1	0	3
Day 7 (n=8)			
No receiving artificial ventilation	1	5	1
No with umbilical arterial catheter	3	5	1
No receiving enteral feeds	4	2	4

*No baby was given enteral feeds on day 1.

systolic and diastolic velocities divided by the mean velocity.)

The significance of the differences in the results from small for gestational age infants and their control groups was assessed by Student's unpaired *t* test. Infants with absent fetal aortic end diastolic frequencies were analysed as a subgroup.

Results

MEASUREMENTS ON THE FIRST DAY

Mean velocity in the superior mesenteric artery was significantly lower in the infants who were small for gestational age (15.0 cm/s) than in

their gestation matched controls (20.4 cm/s, *p*<0.05; fig 1). This was also the case for the mean velocity in the coeliac axis (small for gestational age: 27.0 cm/s; controls: 40.8 cm/s; *p*<0.05). In contrast there was no significant difference between the groups in mean velocity in the anterior cerebral artery.

When the small for gestational age infants with absent end diastolic frequencies in utero were analysed separately the results were more striking. Mean velocity in the superior mesenteric artery was significantly lower in the small for gestational age infants (11.5 cm/s) than in their weight or gestation matched control groups (weight matched: 18.6 cm/s, *p*<0.05; gestation matched: 19.1 cm/s, *p*<0.05). The same was also true for the mean velocity in the coeliac axis (small for gestational age: 23.9 cm/s; weight matched: 34.9 cm/s, *p*<0.05; gestation matched: 44.9 cm/s, *p*<0.05). Again, there were no significant differences between groups in the anterior cerebral artery velocities. Velocity in the superior mesenteric artery of infants who had had absent fetal end diastolic frequencies was significantly lower than in small for gestational age infants in whom end diastolic frequencies had been recorded (11.5 cm/s compared with 21.4 cm/s; *p*<0.01).

The pulsatility index was significantly higher in the superior mesenteric artery and coeliac axis of the infants who were small for gestational age than in their weight matched controls (fig 2; superior mesenteric artery: *p*<0.05; coeliac axis: *p*<0.05). For those infants who had had absent aortic end diastolic frequencies in utero, the pulsatility index was significantly higher than in weight matched (superior mesenteric artery: *p*<0.05; coeliac axis: *p*<0.05) or gestation matched controls (superior mesenteric artery: *p*<0.05; coeliac axis: *p*<0.05).

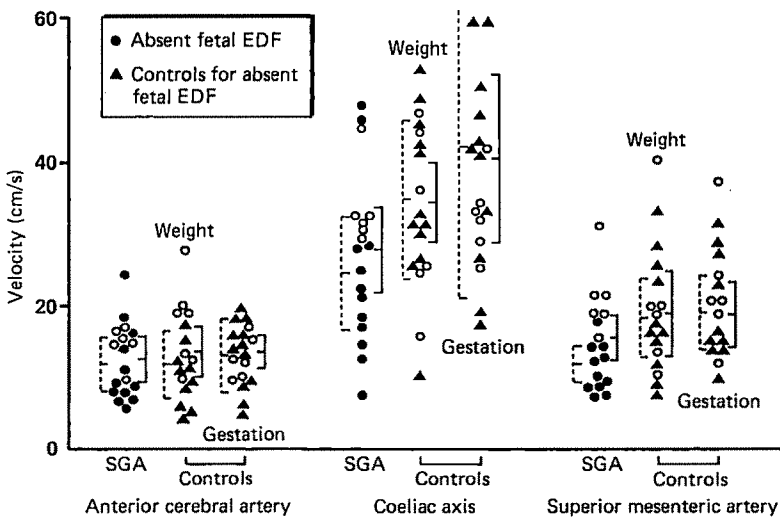


Figure 1 Blood velocity in the anterior cerebral artery, coeliac axis, and superior mesenteric artery during the first day of life in small for gestational age (SGA) infants and their weight matched and gestation matched controls. Means and 95% confidence intervals are shown to the right of each group as solid lines. Small for gestational age infants with absent fetal aortic end diastolic frequencies (EDF) are shown as are their controls. Means and 95% confidence intervals are shown to the left of these subgroups by broken lines.

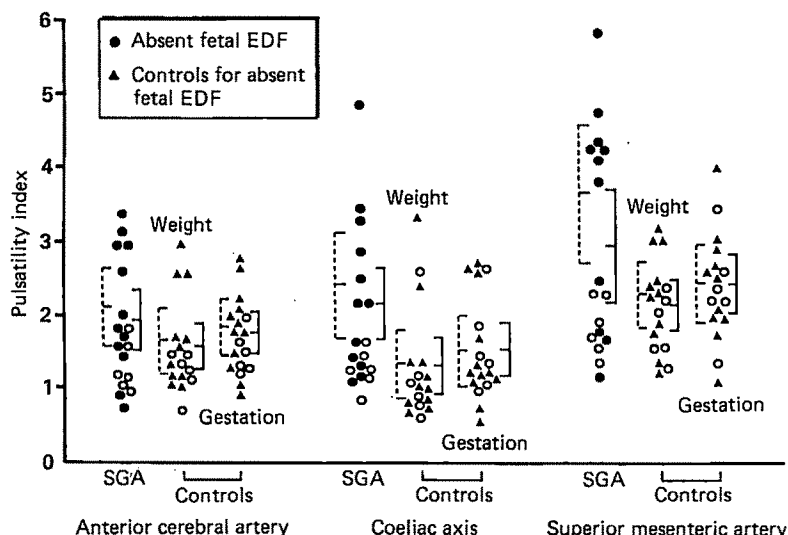


Figure 2 Pulsatility index in the anterior cerebral artery, coeliac axis, and superior mesenteric artery during the first day of life in small for gestational age (SGA) infants and their weight matched and gestation matched controls. Means and 95% confidence intervals are shown to the right of each group as solid lines. Small for gestational age infants with absent fetal aortic end diastolic frequencies (EDF) are shown as are their controls. Means and 95% confidence intervals are shown to the left of these subgroups by broken lines.

MEASUREMENTS ON DAYS 3 AND 7

On day 3, mean velocity in the anterior cerebral artery was significantly higher in infants who were small for gestational age (23.3 cm/s) than in weight matched controls (16.4 cm/s, $p < 0.01$). There were no other significant differences between the groups.

On day 7 the mean velocities in the superior mesenteric artery and the coeliac axis were significantly lower in infants who were small for gestational age than in their gestation matched controls (fig 3; superior mesenteric artery: 21.9 cm/s in small for gestational age infants compared with 33.8 cm/s in controls, $p < 0.05$; coeliac axis: 31.6 cm/s in small for gestational age infants compared with 41.9 cm/s in controls, $p < 0.05$). The mean percentage increase in velocity in the superior mesenteric artery from day 1 was significantly lower in the small for gestational age infants (31%) than in the gestation matched controls (117%, $p < 0.05$).

Discussion

In premature, small for gestational age infants mesenteric and coeliac arterial blood velocity

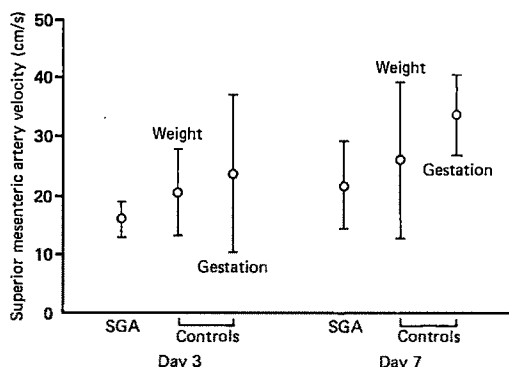


Figure 3 Blood velocity in the superior mesenteric artery on days 3 and 7 in small for gestational age (SGA) infants and their weight matched and gestation matched controls.

was decreased compared with that found in appropriately grown but equally premature infants. These differences are principally accounted for by the group of small for gestational age infants who had absent end diastolic frequencies in the aorta during fetal life. In these infants velocity in the superior mesenteric artery and coeliac axis was lower than in infants of equivalent weight or gestation.

Although low velocity within an artery does not necessarily mean low flow (flow = velocity $\times$ cross sectional area of the vessel), it is unlikely that the small for gestational age infants had significantly larger mesenteric arteries. Indeed, the usual response of a vessel to chronic low velocity blood flow is that of a reduction in diameter of the vessel, which confirms our impression of reduced diameter of the umbilical vessels in many small for gestational age infants. Furthermore, we have found that the superior mesenteric arteries of small for gestational age infants are more difficult to visualise than those of appropriate for gestational age infants, which also suggests that the bore of the mesenteric vessels of small for gestational age infants is narrower than normal.

If we assume that the differences in velocity that we found are associated with similar differences in volume of flow, we could infer that severely growth retarded infants have lower gut blood flow on the first day of life than infants who are appropriate for gestational age. Infants with fetal hypoxia (indicated by absent end diastolic frequencies) are the most severely affected. The differences between the groups cannot be explained by differences in blood pressure, oxygenation, or enteral feeding (table 2); they probably represent a specific defect of visceral perfusion rather than a general perfusion defect, as the velocity in the anterior cerebral artery was similar in all the groups studied. The magnitude of the differences was such that infants with absent fetal end diastolic frequencies had mesenteric artery velocities nearly 40% lower than their controls. Because it has been shown in animals that intestinal oxygen consumption falls when blood flow is decreased by more than 30%,⁴ and that ischaemic tissue injury occurs after a 50% reduction,⁵ the observed changes could have clinically important effects.

The pulsatility index was significantly higher in the superior mesenteric artery and coeliac axis of infants with absent end diastolic frequencies than in either group of controls. This suggests that the infants who were small for gestational age had either a greater amount of left to right ductal shunting,⁶ or an increased impedance to visceral blood flow. We did not attempt to use ultrasound to document the size or incidence of ductal shunting at the time of measurement, but the later incidence of clinical patent ductus arteriosus was lower among small for gestational age infants (4/18) than among weight matched (8/18) or gestation matched (6/18) controls. Increased intestinal vascular resistance is probably the best explanation of our findings.

The higher velocity in the anterior cerebral artery on day 3 in infants who were small for

gestational age may resemble the postanoxic 'luxury' hyperperfusion that is seen in hypoxic-ischaemic encephalopathy.⁷

Mean superior mesenteric artery velocity on the seventh day of life was significantly lower in small for gestational age infants than in gestation matched controls, although similar numbers were receiving enteral feeds. Superior mesenteric artery velocity was much closer to that of the weight matched controls, few of whom were enterally fed. As well as the absolute values being lower, the percentage increase over day 1 values was also reduced. One explanation is that the vascular response to enteral feeding that is seen in normal infants is deficient in severely growth retarded infants,^{8,9} but this warrants further prospective study. A lack of vascular response has been shown in animals that are hypoxic at the time of feeding.¹⁰

Fetuses that are small for gestational age and have absent end diastolic frequencies in the fetal aorta are at increased risk of developing necrotising enterocolitis.³ Our results suggest that the abnormal patterns of perfusion that have previously been shown in fetuses persist into postnatal life, and could result in further hypoxic-ischaemic tissue damage or maturational delay in addition to that which may have occurred in utero. It is possible that the low baseline intestinal blood flow velocity, which

does not increase after enteral feeding, would be unable to meet the additional metabolic demand that such feeding imposes on the gut. We suggest that caution should be exercised when introducing enteral feeds to VLBW infants with severe IUGR, especially to those in whom fetal hypoxia was suspected antenatally.

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Global and depth resolved phosphorus magnetic resonance spectroscopy to predict outcome after birth asphyxia

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Abstract

Twelve normal and 32 asphyxiated neonates were studied using global and depth resolved phosphorus magnetic resonance spectroscopy (^{31}P MRS). Eight of the asphyxiated group died or survived with major neurodevelopmental abnormalities. A global phosphocreatinine/inorganic phosphate (PCr/Pi) ratio below the range of values from normal infants predicted adverse outcome after asphyxia with a positive predictive value of 64%, sensitivity 88%, and specificity 83%. Corresponding values for global inorganic orthophosphate/adenosine triphosphate (Pi/ATP) ratios were positive predictive value 88%, sensitivity 96%, and specificity 88%.

Spatially localised MRS data, obtained using phase modulated rotating frame imaging, showed cerebral energy metabolism to be more abnormal in deep than superficial regions after birth asphyxia. However, in this population of full term infants none of the regional metabolite concentrations were superior to global data for prediction of outcome.

Phosphorus magnetic resonance spectroscopy (^{31}P MRS) is a non-invasive technique that can be used to measure intracellular pH and relative concentrations of phosphorus metabolites *in vivo*.¹ Studies of the brain of normal and asphyxiated infants have shown a characteristic pattern of changes in the brain after an episode of hypoxia-ischaemia.² As would be expected on theoretical grounds, phosphocreatine (PCr) falls and inorganic phosphate (Pi) rises in the postasphyxial brain. The PCr/Pi ratio therefore falls and in severe, usually fatal, cases adenosine triphosphate (ATP) depletion is also seen.³ A previous study comparing the outcome of infants after cerebral hypoxia-ischaemia to neonatal MRS results has shown that a low PCr/Pi ratio is highly predictive of poor outcome (positive predictive value 93%) but that some infants with a normal PCr/Pi also had a poor outcome.³ The limited sensitivity of that study (74%) could perhaps be attributed to the fact that conventional surface coil spectroscopy lacks any significant degree of spatial discrimination.

Phase modulated rotating frame imaging (PMRFI) is a modification of MRS that provides depth resolved biochemical data.⁴ We have previously reported a correlation between PMRFI results and severity of encephalopathy after birth asphyxia.⁵ The aim of the present study was to determine whether spatially localised PMRFI data improved the accuracy of global MRS for the prediction of death or

handicap in a larger group of asphyxiated infants.

Patients and methods

Full details of the MRS methods are described elsewhere.⁵ Studies were performed without sedation over a period of 30-45 minutes, usually after a feed. Major movements of the infant's head position during PMRFI were unusual, but did necessitate restarting data collection. The infant was positioned prone in the bore of a 1.9 tesla superconducting magnet, with the right side of the head resting on a foam pillow into which a surface coil was incorporated. The surface coil consisted of a 15 cm diameter transmitter and a 6.5 cm diameter receiver coil, and received ^{31}P MRS signals at a frequency of 32.7 MHz from temporoparietal brain. Two conventional 'pulse and collect' sequences (64 pulses, duration 275 μs , interval 3s) were recorded and, after profile correction and Fourier transformation, a 'global' spectrum was obtained. Figure 1(a) shows a typical global spectrum from a normal infant, with the peak assignments, and fig 2(a) shows a comparable global spectrum from a severely asphyxiated infant. Relative metabolite concentrations were calculated from spectra using a computer assisted curve fitting programme.

Depth resolved data were then obtained using PMRFI, which utilises the linear radiofrequency field produced by the transmitter coil to spatially encode spectral data.⁶ Three spectra were taken for analysis from each infant, from the data matrix produced by PMRFI. Each spectrum is derived from an approximately disc shaped volume of brain. Approximately 90% of the signal contributing to each spectrum comes from a disc of 1 cm depth and the same diameter as the receiver coil. Superficial, middle, and deep spectra were analysed, corresponding to signal from brain approximately 0-1, 1-2, and 2-3 cm below the skull. Figures 1(b), (c), and (d) show depth resolved spectra from a normal newborn and figs 2(b), (c), and (d) are comparable spectra from a severely asphyxiated infant.

Complete global and depth resolved data sets were recorded from 12 normal infants, gestation 38-42 weeks, Apgar scores 5-10 at 1 minute and 9-10 at 5 minutes, studied at 1-5 days old. Similar data were recorded from 32 infants studied after birth asphyxia. The table shows clinical details of the asphyxiated infants. Because of the small number of normal studies, values for metabolite ratios from asphyxiated infants were compared with the entire range of

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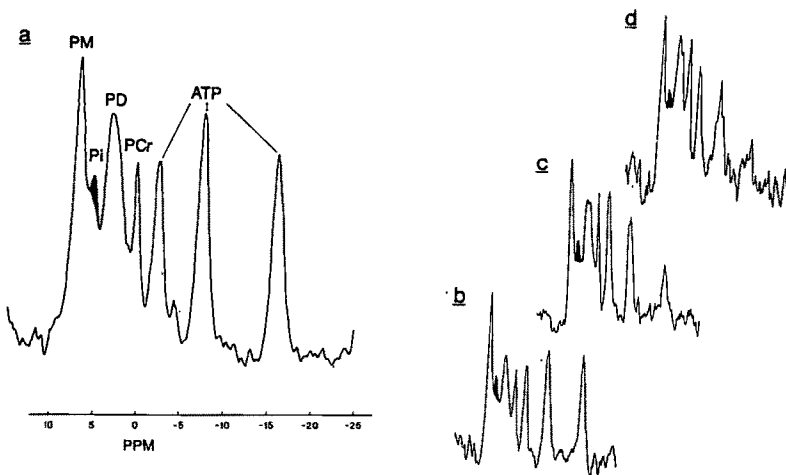


Figure 1 Global (a), and spatially localised magnetic resonance spectra from superficial (b), middle (c), and deep (d) regions of the brain of a normal infant. See text for details of localisation. Peak assignments are—ATP: adenosine triphosphate, PCr=phosphocreatine, PD=phosphodiester and phospholipid bilayers, Pi=inorganic orthophosphate, PM=phosphomonoesters. The three ATP peaks are β , α , and γ from right to left. β ATP may be underestimated on regional data for technical reasons.

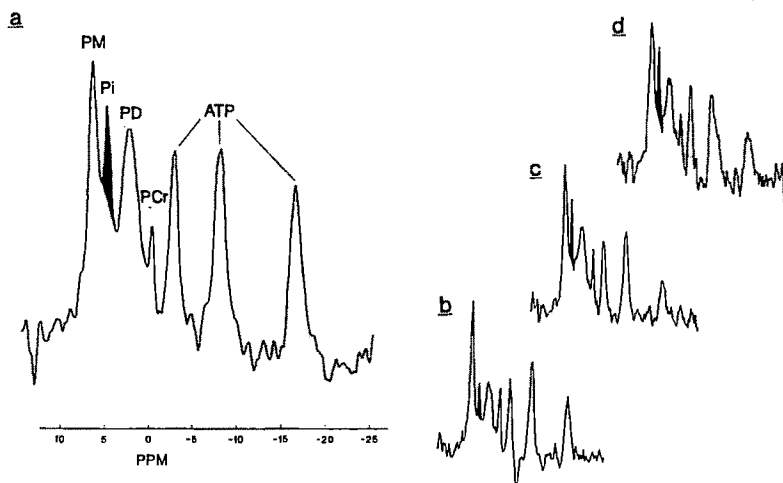


Figure 2 Global (a), and spatially localised (b), (c), and (d) magnetic resonance data from the same regions as fig 1, from an asphyxiated baby with an adverse outcome studied at 4 days. Peak assignments are—ATP: adenosine triphosphate, PCr: phosphocreatine, PD: phosphodiester and phospholipid bilayers, Pi=inorganic orthophosphate, PM: phosphomonoesters. The three ATP peaks are β , α , and γ from right to left. β ATP may be underestimated on regional data for technical reasons.

Clinical details of asphyxiated infants. Results are median (range)

	Normal outcome (n=24)	Adverse outcome (n=8)
Gestation (weeks)	40 (35–42)	41 (36–42)
Age at MRS (days)	3 (1–6)	9 (3–16)
Apgar score		
1 minute	2 (0–7)	2 (0–5)
5 minutes	6 (0–10)	4 (0–8)
Cord artery pH	7.02 (6.66–7.26)	6.94 (6.68–7.10)
Cord artery base deficit (mmol/l)*	19 (9–28)	21 (14–28)
Survivors, major handicap	0	2
Neonatal deaths	0	4
Postneonatal deaths	0	2

*Cord artery blood gases were available on 22 normal and six adverse outcome infants.

values from normals, rather than using standard deviations or confidence intervals.

All but two of the asphyxiated infants who survived the neonatal period were assessed neurodevelopmentally at regular intervals in hospital follow up clinics. The other two infants did not attend the hospital clinic but were assessed as completely normal on health visitor assessment at 18 months.

The study was approved by the Central Oxford Research Ethics Committee and the parents of all infants gave informed consent. Normal infants were recruited by discussing the project with groups of parents during antenatal classes. These parents were invited to contact the investigators via their midwife in the post-natal period.

Results

Eight asphyxiated infants had an adverse outcome. Four died in the neonatal period and two others, both severely neurologically abnormal, died at 11 weeks and 19 months. Two survived with major cognitive deficits and spastic quadriplegia at 37 and 38 months. Twenty four asphyxiated infants, now age 15–43 (median 31) months were neurodevelopmentally normal at their last assessment at 9–19 (median 13) months.

Global PCr/Pi and Pi/ATP ratios for all infants are shown in fig 3(a) and (b), which

Global PCr/Pi

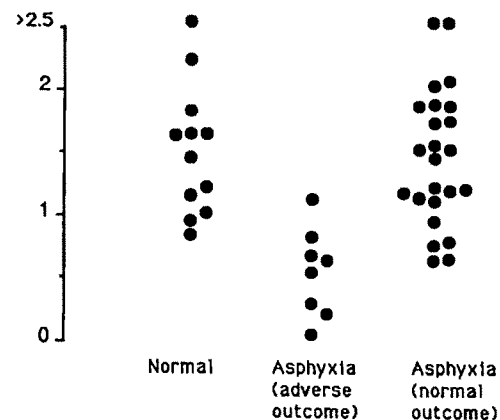


Figure 3 (a) Global PCr/Pi ratios from normal infants and asphyxiated infants divided into groups according to outcome. Infants with adverse outcome differ from normals (Mann-Whitney test, $p<0.002$) and from asphyxiated infants with good outcome ($p<0.001$).

Global Pi/ATP

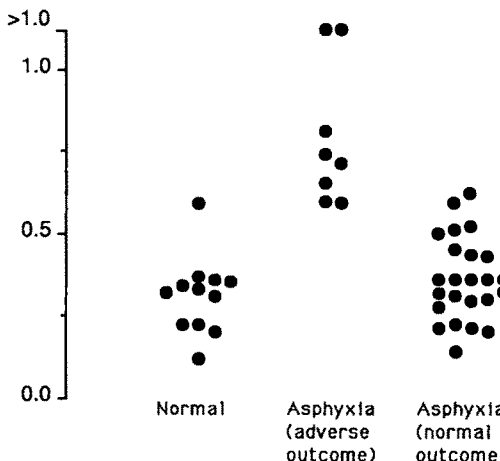


Figure 3 (b) Global Pi/ATP ratios from normal infants and asphyxiated infants divided into groups according to outcome. Infants with adverse outcome differ from normals (Mann-Whitney test, $p<0.002$), and from asphyxiated infants with good outcome ($p<0.001$).

show no significant differences in metabolite ratios between normal infants and those asphyxiated babies with a good outcome. The infants with adverse outcome form a population with a lower PCr/Pi and higher Pi/ATP ratio. Only one asphyxiated infant with adverse outcome had PCr/Pi in the range of normals. There were fewer 'false positive' results from infants with a normal outcome using Pi/ATP ratio as a predictor. Sensitivity, specificity, and positive predictive value for the prediction of death or handicap were 88%, 83%, and 64% respectively for PCr/Pi and 88%, 96%, and 88% for Pi/ATP.

Depth resolved PMRFI data for Pi/ATP are shown in fig 4(a), 4(b), and 4(c). Figure 4(a) shows a wide variation in superficial metabolite ratios from all infants. Spectra from middle and deep regions, shown in fig 4(b) and (c), show a significant difference between the adverse outcome group and normal infants or asphyxiated infants with a normal outcome. Depth resolved data did not, however, show any increased discrimination compared to global data. The best PMRFI discriminator was the PCr/Pi ratio from 2–3 cm below the skull, with sensitivity, specificity, and positive predictive value of 75%, 92%, and 75%.

Discussion

The majority of infants with clinical and biochemical evidence of birth asphyxia will either show no evidence of neurological abnormality in the newborn period or will exhibit only a mild encephalopathy.⁷ However a minority, about two infants per 1000 livebirths, will develop a moderate or severe hypoxic-ischaemic encephalopathy with seizures and nervous system depression which is variable in degree and duration.⁸ This group of infants has an approximately 50% incidence of adverse outcome, either death or significant neurodevelopmental delay.⁷

Rational management in the immediate neonatal period, when multiorgan failure requires intensive life support, would be greatly assisted if accurate prognostic tools were available. Simple clinical assessments of encephalopathy grading⁷ and time to attain sucking feeds⁹ are very predictive but retrospective and may be altered by drug treatment. Conventional techniques such as computed tomography¹⁰ and ultrasound¹¹ tend to show definitive changes after the first week of life. Earlier objective evidence of severe irreparable brain damage is important if parents are to be accurately counselled about

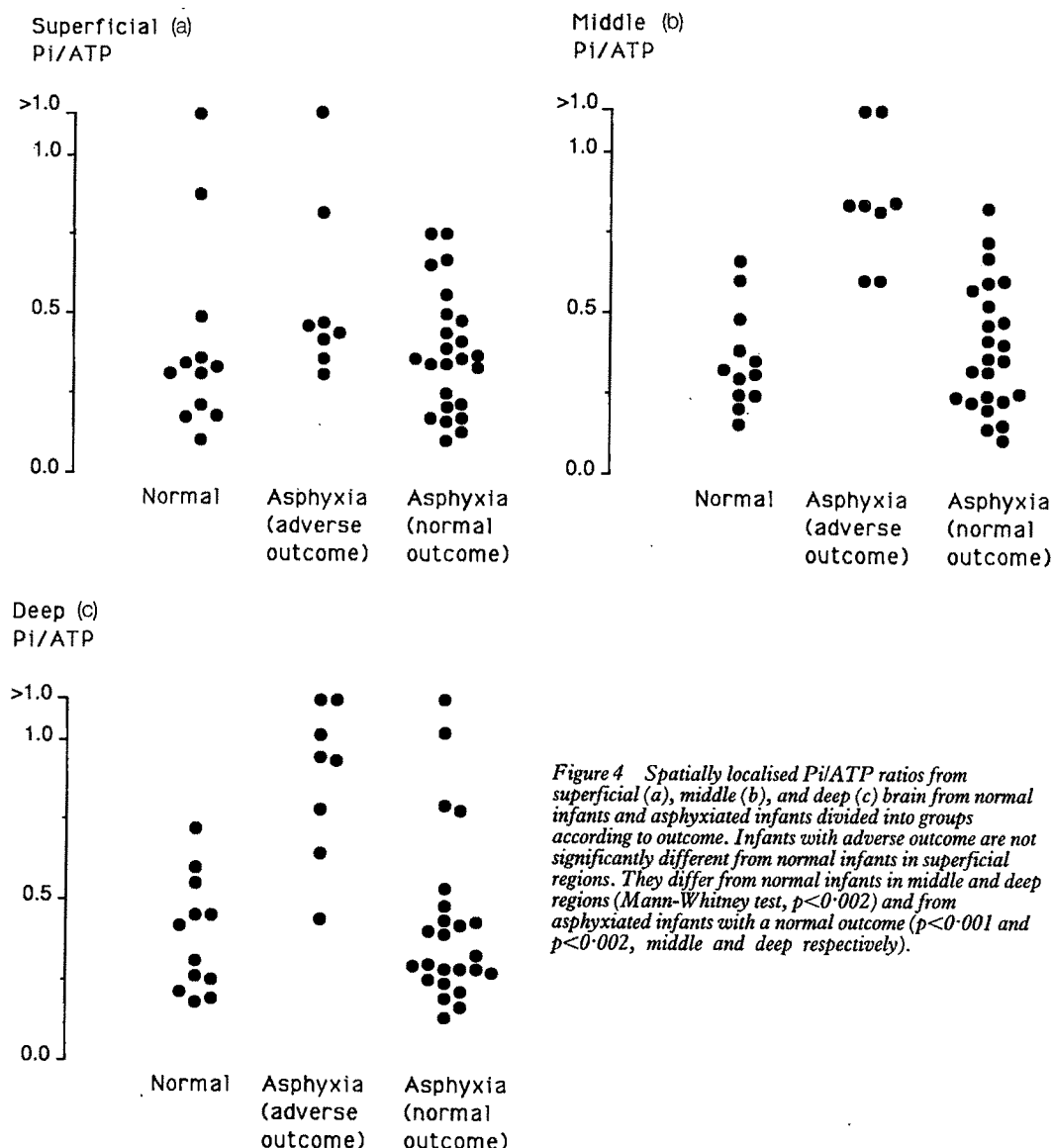


Figure 4 Spatially localised Pi/ATP ratios from superficial (a), middle (b), and deep (c) brain from normal infants and asphyxiated infants divided into groups according to outcome. Infants with adverse outcome are not significantly different from normal infants in superficial regions (Mann-Whitney test, $p < 0.002$) and from asphyxiated infants with a normal outcome ($p < 0.001$ and $p < 0.002$, middle and deep respectively).

the wisdom of pursuing intensive care in the first few days of life. Doppler studies of cerebral artery blood flow velocities,¹² electroencephalography,⁸ ³¹P MRS,³ and more recently near infrared spectroscopy¹³ have been used to assess cerebral status at an early stage, when clinical signs are often heavily masked by sedative and anticonvulsant drugs.

Azzopardi *et al* have shown that conventional ³¹P MRS within the first week of life has a high specificity and positive predictive value for the prediction of adverse outcome, so an abnormal magnetic resonance spectrum is clinically helpful. However, a normal PCr/Pi ratio is not necessarily reassuring, as reflected in the limited sensitivity reported in their study.³ Neonates with apparently normal cerebral energy metabolism in the postasphyxial period may later manifest symptoms suggestive of neuronal damage. The reason may be that conventional surface coil spectroscopy detects magnetic resonance signals from a large and ill defined volume of brain tissue, and the spectrum may be heavily biased by the high signal from superficial tissues. Regions of impaired energy metabolism may therefore escape detection in the global spectrum, especially if they lie deeper in the brain.

PMRFI is one of a variety of techniques for spatial localisation of MRS data,¹⁴ and its use for the investigation of regional cerebral metabolism in the neonate has been fully described in relation to severity of neonatal encephalopathy.⁵ That study showed that the maximum region of energy impairment in severely asphyxiated full term infants corresponds approximately to subcortical white matter, and suggested that localised spectra from this particularly vulnerable region should be of greater prognostic value than global data. The present study explores that hypothesis by comparing global and regional metabolite ratios as indicators of short term neurodevelopmental outcome for a group of asphyxiated neonates. Only one hemisphere was studied, as none had ultrasound evidence of focal abnormality or asymmetry. There are obvious limitations to this study in respect of the small numbers of subjects, especially controls, and the short duration of follow up. Ninety two percent of asphyxiated infants have received regular clinical examinations in hospital based follow up clinics, but have not been psychometrically or neurodevelopmentally assessed by independent observers, and the youngest are only 15 months old. It is therefore possible that mild or even moderate neurodevelopmental deficits, especially in cognitive areas, may subsequently become apparent in the group designated as having a normal outcome in this study. However, infants in this group are very unlikely to have significant cerebral palsy, in contrast to the adverse outcome group, of whom the two survivors both have severe cognitive and motor deficits.

Figure 3(a) confirms previous studies that show that a low global PCr/Pi ratio, implying impaired cerebral energy metabolism, is strongly associated with adverse outcome. In this study, global Pi/ATP ratio seemed to discriminate

slightly better than PCr/Pi between the groups of asphyxiated infants with normal and adverse outcome. This unexpected finding may result from the small numbers of infants in this study. Theoretically, PCr concentrations would be expected to fall before ATP depletion occurred, so the PCr/Pi ratio should be a more sensitive index of abnormality than Pi/ATP ratio. In this study, only one severely asphyxiated infant showed significant ATP depletion. This infant was studied at 3 days and died at 6 days and the magnetic resonance spectra was grossly abnormal with no detectable PCr or ATP. As reported previously in a smaller group of infants, spatially localised data clearly show a wide variation in metabolite ratios from superficial brain in both normal and asphyxiated infants.⁵ This is unlikely to be artefactual because the superficial PMRFI spectra have the best signal to noise ratio. Energy impairment was most apparent in deeper brain tissue in the group with subsequent adverse outcome. The sample volumes interrogated to provide the depth resolved spectra do not conform to anatomical boundaries, so it is impossible to be precise about which tissues are represented in each spectrum. Superficial spectra will contain signals from cortex as well as subcortical white matter, middle spectra will represent predominantly subcortical white matter, and deep spectra will also contain signals from periventricular areas.

Prognostic sensitivity of the global metabolite ratios was high and was not improved by obtaining regional information using PMRFI. Only one infant with an adverse outcome had global PCr/Pi and Pi/ATP ratios in the normal range, perhaps because the MRS study was delayed until 9 days. All the spatially localised metabolite ratios from that infant were also within normal limits. These results confirm that conventional ³¹P MRS can be a useful prognostic technique after birth asphyxia. In this small study of full term infants, the depth resolved information provided by PMRFI did not improve prediction of adverse outcome.

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Aspirin to prevent fetal growth retardation

The underlying placental dysfunction is apparently similar in pre-eclampsia and in idiopathic fetal growth retardation, with placental vascular disease and abnormalities of prostaglandin and thromboxane production. Low dose aspirin could help by its effect on intravascular thrombosis and on thromboxane concentrations, low concentrations of thromboxane being associated with decreased pressor response to angiotension II.

A recent French multicentre trial (S Uzan and colleagues, *Lancet* 1991;337:1427-31) has shown that low dose aspirin reduces the incidence of fetal growth retardation and of maternal proteinuria.

Patients were enrolled into the trial at 15 to 18 weeks of pregnancy. All had had either fetal growth retardation in their one previous pregnancy or a poor outcome in two previous pregnancies, at least one of which was fetal growth retardation, poor outcome being defined as a small for dates baby, fetal death, or placental abruption. When those given placebo were compared with those treated with either aspirin alone or aspirin plus dipyridamole, the mean birth weight was significantly lower in the placebo group (2526 g v 2751 g, $p=0.029$, 95% confidence interval for difference 129 to 321 g). The mean duration of pregnancy was 36 weeks six days in the placebo group and 37 weeks five days in the treated group ($p=0.05$). Fetal growth retardation occurred in 26% of patients given placebo and 13% of those given treatment. Fetal death and placental abruption were also less common in the treatment group but the numbers were small and the differences did not reach statistical significance. There was, however, a significant reduction in maternal proteinuria (11% v 3% $p<0.02$). The greatest effect of treatment was seen in those mothers who had had a poor outcome in more than one previous pregnancy. A separate trial of aspirin alone against aspirin plus dipyridamole showed no significant differences.

Although the results seem encouraging, the authors are very cautious. They clearly fear misuse of their findings and their conclusion is worth quoting: 'thus, it now seems justifiable to propose aspirin treatment for any patient considered at high risk, even if in her first pregnancy. On the other hand, massive use of aspirin by millions of pregnant women yearly certainly cannot be recommended'.

ARCHIVIST

Otoacoustic emissions and auditory brainstem responses in the newborn

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Abstract

The auditory function of 370 infants, drawn from both low and high risk groups, was tested before postnatal discharge using three tests: standard auditory brain stem responses (ABR), automated analysis of ABR, and automated analysis of evoked otoacoustic emissions (OAE). All infants failing any neonatal test had further audiological evaluation. Follow up information was also available on those who passed neonatal tests. Automated OAE testing of both ears was quickest (median 12.5 minutes) and least invasive (no scalp electrodes). Bilateral failure rates (and upper 95% confidence limits) with a stimulus 35-36 dB above normal hearing threshold level (nHL) were 3.0% (4.6) with automated OAE, 3.2% (5.1) with ABR, and 2.7% (4.4) with automated ABR. Automated OAE was the test most sensitive for subsequently confirmed hearing impairment. Sequential testing with automated OAE followed, in those failing this test, by automated ABR would have provided a screening test for substantial hearing impairment with a specificity greater than 99% in this population. Possible application as a universal screen is discussed.

Children with severe to profound congenital hearing impairment—that is, a hearing loss >60 dB relative to normal hearing threshold level (nHL)—will not develop speech and language normally. This impairment and the secondary cognitive and behavioural consequences can be devastating. There is some evidence that early rehabilitation is effective in reducing this impairment.¹ The aim of an infant hearing screening programme should be to detect severe to profound hearing losses and to reduce the age at which intervention is begun.²

The American Academy of Pediatrics published a 'position statement' in 1982 which recommended that screening of infants at high risk of hearing impairment should be completed by 3 months and habilitation begun by 6 months of age.³ Screening of high risk groups rather than all infants was recommended. Indeed universal screening of hearing has never been widely adopted in North America. Unfortunately less than half of all severe/profound hearing losses occur in infants with the current high risk factors: a recent thorough application of distraction testing to a cohort of high risk infants (weighing <2000 g at birth or admitted to a special care baby unit for >24 hours) in the Oxford region was reported to be

ineffective because 71% of infants in that birth cohort who were registered as hearing impaired before the age of 3 years were not in the 'at risk' group.⁴ This presents a strong argument in favour of broadening the definition of 'high risk' or introducing universal screening.

In the UK universal screening is currently performed in the form of distraction testing at 8 months. Although explicit guidelines for parents, direct access to audiology services, and improved health visitor training can help,⁵ the sensitivity and specificity of this test remain unacceptably low in most districts.⁶⁻⁷ Throughout the European Community, more than half of bilateral hearing losses of more than 50 dBnHL in the better ear remain undetected by the age of 3 years.⁸ Even in that minority who are detected by distraction testing, the diagnostic process is rarely complete before the age of 1 year so that intervention is necessarily delayed.

Neonatal testing offers the opportunity for earlier diagnosis and intervention. Automated behavioural tests such as the auditory response cradle⁹ have not been sufficiently sensitive or specific to succeed as screening tools.¹⁰⁻¹¹ The auditory brain stem response (ABR) is established as a sensitive test for auditory dysfunction in the neonatal period with specificity which can be high provided testing is deferred until term and/or recovery from acute illness.¹² Unfortunately ABR testing requires too much time per test and too much specialised training in interpretation to be suitable for universal screening. Automated analysis of ABR may help overcome these drawbacks.

The discovery of otoacoustic emissions (OAE)¹³ and their subsequent application to newborn infants¹⁴⁻¹⁶ has opened a possible new avenue to quick and reliable screening. We report here our experience of automated analysis of both ABR and evoked OAE in comparison both with standard ABR and with subsequent hearing assessment in high risk and low risk newborns. Possible application of these tests as part of a universal neonatal screening test is discussed.

Patients and methods

The infants studied were inpatients at Princess Anne Hospital, Southampton, which has an annual rate of 5500 deliveries representing 90% of all deliveries in the Southampton health district. The Department of Neonatal Medicine incorporates a special care baby unit. This unit has six intensive care cots including the only two regionally funded cots in the Wessex region.

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Three objective methods of evaluating auditory function were evaluated in three groups of neonates. (1) Low risk group: full term babies at low risk of deafness. (2) Special care baby unit group: those, other than group 3 below, admitted to the unit for more than 48 hours. (3) Family history or craniofacial malformation group: babies at increased risk of hearing impairment because of craniofacial deformity or a family history of deafness.

Both ears of each baby were tested by the following methods:

(1) ABR: measurement of ABR produced by series of clicks at 36, 45, and 60 dBnHL was made via three scalp electrodes, an averaging computer, and a printer. The presence and latency of the ABR were determined by a trained observer.

(2) Automated ABR analysis: the ABR produced by a series of clicks at 35 dBnHL was detected as in (1), compared with a stored template of an ABR, and the response designated as 'pass' or 'refer' by an automated analyser (marketed as Algotek or Algo-1).

(3) Automated OAE analysis: OAE after presentation of clicks at 16, 26, and 36 dBnHL were detected by a microphone within the same probe used to present the clicks in the canal of the external ear. Programmable otoacoustic measurement system (POEMS) software¹¹ was used with an averaging computer to determine whether an emission was detectable. Evoked OAE were considered present if a visual display showed a response which was both visible on the screen and fulfilled statistical criteria calculated by POEMS. (Criteria were: (i) F_{sp}^* of signal in each series of computer-averaged emissions >2 and (ii) correlation coefficient between two series of computer averaged emissions >0.5 .) The automated OAE analysis by POEMS controls all the test parameters and will provide prompts for the tester to follow in order to complete the test procedure quickly, simply, and in a standardised way. Different testers can therefore be employed with minimal training.

Additional information on the clinical history of the infant and on middle ear function (immittance) was also recorded in a standardised database. Subsequent follow up on all tested babies included the results of distraction testing at 8 months, questionnaires to the families when the child was 18 months' old, and the results of subsequent assessment in any tested baby seen at the District Preschool Hearing Clinic or the Wessex Regional Audiology Clinic. In addition, all babies failing any neonatal test and a random sample of those who passed had the neonatal tests repeated at the age of 3 months. All babies failing at 3 months were referred for a full audiological evaluation at the Wessex Regional Audiology Clinic.

The aim of the testing procedures was to detect hearing impairment of a degree likely to interfere substantially with the development of speech and language. We defined such 'substantial' hearing impairment as moderate (>40

dBnHL) or greater hearing loss in the better ear. Crude failure rates on neonatal tests were derived. The significance of differences between percentage failure rates (%diff) in the three groups of babies on a particular neonatal test was examined by calculating the standard error of the difference between the percentage failure rates (SE %diff). If %diff - SE %diff is greater than 2, then $p < 0.05$ that the difference arose by chance.

The false positive rate (that is, test failure without subsequently confirmed substantial hearing impairment), expressed as a percentage, is equal to 100 minus the specificity, expressed as a percentage. The percentage of false positives (and upper 95% confidence limit) for substantial hearing impairment was calculated for each test by subtracting cases of subsequently confirmed substantial hearing impairment from the crude failure rates. Cases in whom follow up assessment of hearing by audiology services was incomplete were assumed not to be hearing impaired for the purpose of specificity calculation, tending to underestimate the specificity of the failed neonatal test.

Results

Three hundred and seventy babies were tested and follow up, including results of distraction testing, is available on the first 354. Testing on the low risk babies ($n=86$) and those with a family history or craniofacial malformation ($n=61$) was carried out at a median (quartiles) postconceptional age of 39 (38.3-41) weeks. For babies in the special care baby unit group ($n=223$) median birth weight was 2130 g and median gestational age was 34 (32.5-37) weeks at birth and 37 (36-39) weeks at testing.

Practicability as reflected in test duration was compared between neonatal tests. Automated OAE took a median (5th and 95th centiles) time of 7.2 (5.8-12.5) minutes. Electrode placement, required for ABR and automated ABR but not for automated OAE, took 12.5 (8.4-21) minutes. The additional testing time was less for automated ABR (1.5 (0.4-9.8) minutes) than for ABR (7.5 (6.7-11.8) minutes). For the latter test only, additional time and skills were needed to interpret the printed ABR. Testing with ABR, automated ABR and automated OAE was completed in 719, 699, and 714 ears respectively with neither ear tested in two (0.5%), 10 (2.7%), and six (1.6%) babies respectively. Failure to test either ear was attributable to failure of the baby to settle in none, nine, and four babies respectively with equipment failure accounting for the remainder. The number of such failures was undoubtedly increased by the need to complete all three types of testing plus immittance measurement in every infant in a single session.

FAILURE RATES

Failure rates (upper 95% confidence limit) for detection of an OAE in either ear after presentation of a 26 or 36 dBnHL stimulus were 4.6% (6.8) and 3.0% (4.6) of all 370 infants tested respectively. Equivalent figures for

*The F_{sp} is the F statistic for sound pressure level and provides a measure similar to signal-to-noise ratio.

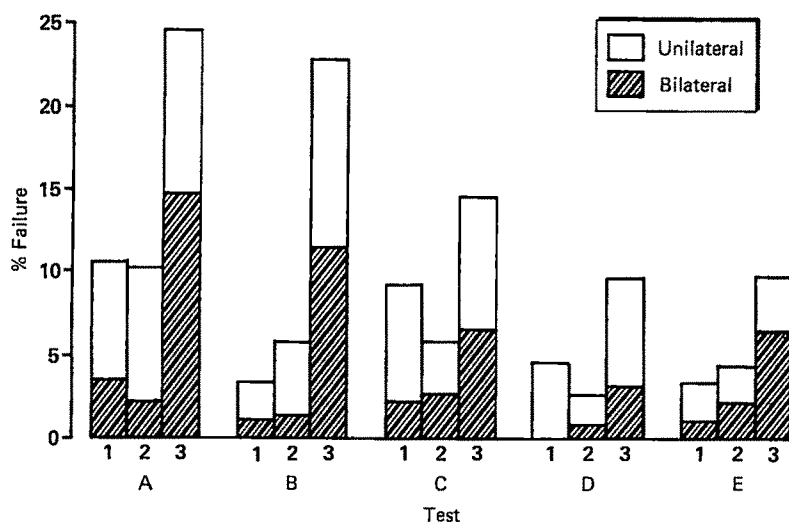


Figure 1 Percentage of infants failing a neonatal hearing test. Groups: (1)=low risk ($n=86$), (2)=special care baby unit infants (excluding group (3)) ($n=223$), and (3)=craniofacial malformation or family history of deafness ($n=61$). Tests: (A)=automated OAE analysis with 26 dBnHL stimulus; (B)=automated OAE analysis with 36 dBnHL stimulus; (C)=conventional ABR with a 35 dBnHL stimulus; (D)=conventional ABR with a 45 dBnHL stimulus; and (E)=automated ABR analysis with a 35 dBnHL stimulus.

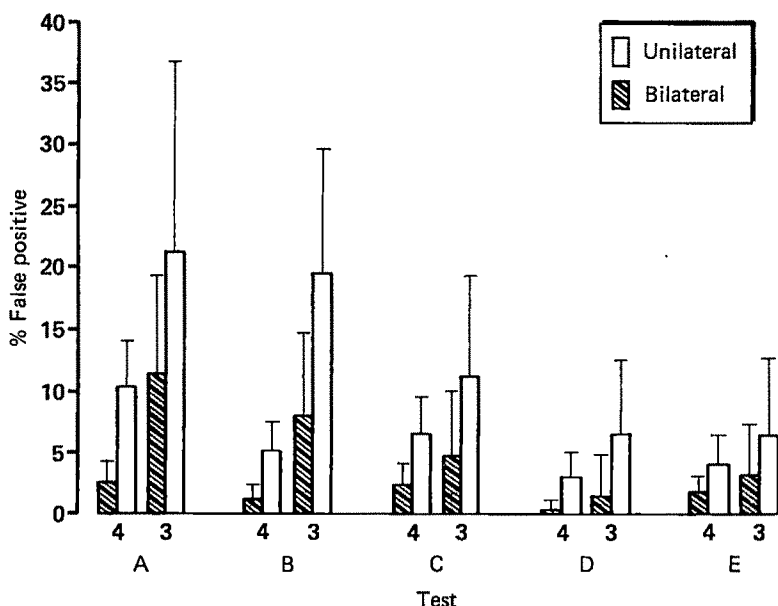


Figure 2 Percentage (with upper 95% confidence limit) of infants failing a neonatal hearing test without subsequent confirmation of substantial hearing impairment (that is, false positive rates). Groups: (4)=low risk plus special care baby unit infants (excluding group (3)) ($n=309$) and (3)=craniofacial malformation or family history of deafness ($n=61$). Tests: (A)=automated OAE analysis with 26 dBnHL stimulus; (B)=automated OAE analysis with 36 dBnHL stimulus; (C)=conventional ABR with a 35 dBnHL stimulus; (D)=conventional ABR with a 45 dBnHL stimulus; and (E)=automated ABR analysis with a 35 dBnHL stimulus.

percentage failure on ABR at 35 and 45 dBnHL and for automated ABR screening at 35 dBnHL were 3.2% (5.1), 1.1% (2.2), and 2.7% (4.4) respectively. Failure rates in the special care baby unit and low risk groups were very much alike ($\%diff < SE \%diff$) while the babies who had a family history or craniofacial malformation had higher failure rates on all neonatal tests (fig 1). Because of the very similar failure rates in special care baby unit and low risk groups, these groups have been combined for the purpose of subsequent calculations of percentage failures and false positives (see discussion). Failure rates on automated OAE were significantly higher in the group with a family history or craniofacial

malformation compared with the combined special care baby unit/low risk group ($\%diff > 2 \times SE \%diff$, $p < 0.05$ with either a 26 dB or a 36 dB stimulus and with either unilateral or bilateral testing). ABR and automated ABR showed similar trends ($\%diff > SE \%diff$ and $< 2 \times SE \%diff$ with all tests).

False positive rates as defined (see methods) are shown as percentages with upper 95% confidence limits for unilateral and bilateral testing in fig 2.

SENSITIVITY

Sensitivity of the neonatal tests for subsequently confirmed hearing loss was also examined. Thirteen cases of persistent hearing impairment were identified among the infants tested. Three came within our definition of substantial hearing impairment (see methods) (table). The remaining 10 had lesser degrees of impairment as detailed in the table and were included with infants who were not hearing impaired among the 'false positives' for those neonatal tests which they failed. Of these 10, three infants who passed all neonatal tests were found to have persistent mild bilateral hearing impairment secondary to middle ear problems after failing distraction testing at 8 months (table). All three had normal immittance and tympanometry at the time of neonatal testing. The remaining seven infants with mild or moderate hearing impairments had all failed automated OAE in the neonatal period.

Questionnaires on hearing were sent to families of all 275 infants tested who have reached the age of 18 months and were completed by 210 (76%) of these. Neither questionnaires nor distraction testing by health visitors at 8 months uncovered any other cases of hearing impairment nor did they come to district or regional audiology clinics by other routes.

PERFORMANCE OF TESTS IN COMBINATION

Combinations of neonatal tests were considered. Automated OAE, being much the quickest and most convenient test, was the only possible contender as a universal screening tool and automated ABR was otherwise the test requiring the least time and skill and was highly specific (fig 2). Failure rates from a two stage screening procedure in which all automated OAE failures were screened with automated ABR were therefore derived for the same study population (fig 3). It is apparent that bilateral testing with automated OAE at either 26 dBnHL or at 36 dBnHL followed by either unilateral or bilateral testing with automated ABR offers screening with an upper 95% confidence limit for 'false positive' failure of less than 1% (that is, a specificity with a lower 95% confidence limit of $> 99\%$).

Discussion

The suitability of a test for screening is dependent upon its specificity, sensitivity, and practicality. This study aimed to determine specificities of neonatal tests of auditory function for

Results in all hearing impaired infants

Patient No	Group	Outcome hearing loss		Neonatal test results (left/right)				Distraction test at 8 months
		Severity (left/right)	Type	Automated OAE*	ABR*	Automated ABR	Immittance and tympanometry	
Substantial hearing impairment								
1	Craniofacial malformation	40–60/40–60	Bilateral atresia	>>36/>36	60/>60	Fail/fail	Obstructed	Not tested
2	Family history	90/90	Sensorineural	>36/>36	?/>60	Fail/fail	Normal	Not tested
3	Craniofacial malformation	60–90/40–60	Sensorineural and bilateral atresia	>36/36	60/>60	Fail/fail	Obstructed	Not tested
Mild hearing impairment								
4	SCBU	20–40/20–40	Conductive	Pass	Pass	Pass	Pass	Fail‡
5	Family history	20–40/none	Conductive	36/pass	35‡/pass	Pass/pass	Pass/pass	Not tested
6	Craniofacial malformation	20–40/20–40	Conductive	26/26	35‡/35‡	Pass/pass	Pass/pass	Pass
7	Family history	20–40/20–40	Conductive	Pass	Pass	Pass	Pass	Fail‡
8	SCBU	40–60/20–40	Conductive	26/>36	?/?	Fail/pass	Flat/flat	Not tested
9	Craniofacial malformation	20–40/20–40	Conductive	Pass/26	Pass/pass	Pass/pass	Pass/pass	Fail
10	Craniofacial malformation	20–40/40–60	Conductive	26/36	45/45	Pass/fail	Pass/pass	Fail
11	SCBU	20–40/20–40	Conductive	Pass	Pass	Pass	Pass	Fail‡
12	Craniofacial malformation	20–40/40–60	Conductive	Pass/26	Pass/pass	Pass/pass	Flat/flat	Fail
13	SCBU	20–40/20–40	Conductive	Pass/26	45/60	Fail/fail	Pass/flat	Fail

*Results given as minimum stimulus intensity in dBnHL at which ABR or OAE (POEMS) was recorded.

†ABR present but wave latencies prolonged.

‡All infants except these three were known by health visitors to be attending audiology clinics when tested at 8 months.

SCBU: special care baby unit.

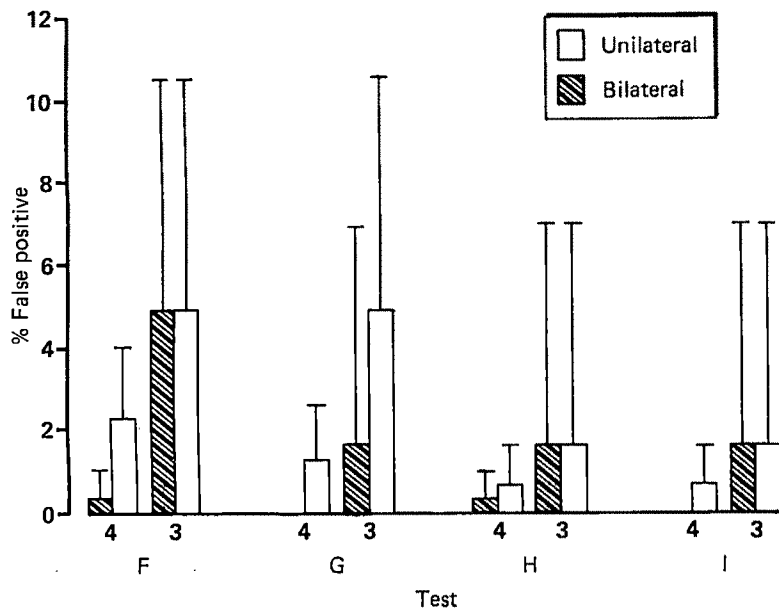


Figure 3 Percentage (with upper 95% confidence limit) false positive rates on sequential combinations of neonatal tests. Groups: (4) low risk plus special care baby unit infants (excluding group (3)) (n=309) and (3) craniofacial malformation or family history of deafness (n=61). Tests: (F)=automated OAE analysis with 26 dBnHL stimulus plus unilateral failure on automated ABR; (G)=as (F) but with 36 dBnHL stimulus for OAE; (H)=automated OAE analysis with 26 dBnHL stimulus plus bilateral failure on automated ABR; and (I)=as (H) but with 36 dBnHL stimulus for OAE. In the figure unilateral and bilateral refer to failure on automated OAE analysis.

severe hearing impairment but some observations about the other two parameters are also possible.

SPECIFICITY

Given that over three quarters of our study population were at increased risk of hearing impairment, the overall bilateral (unilateral) failure rates using automated OAE were low at approximately 6% (13%) and 3% (8.1%) with a 26 and 36 dBnHL stimulus respectively and these rates were reduced by more than half in both low risk and special care baby unit subgroups (fig 1).

These figures compare favourably with failure rates on a first and on both a first and a second 8

month distraction test of 16.3% and 6.8% respectively in a cohort of unselected children and of 18.3% and 3.2% respectively in a population of babies from a special care baby unit.⁴⁻⁶ An onward referral rate of 2.6-6.6% after failure on distraction testing over an entire health district was reported by Scanlon and Bamford.⁷ The failure—or test abandoned—rate on a first test using the Linco-Bennett auditory response cradle was also higher at 7.9% and 10.5% in two reports on both low risk and special care baby unit infants⁹⁻¹¹ and was 21% in a population from a special care baby unit.¹⁰

Others have reported that emissions can be recorded in 98-100% of normal infants.¹⁴⁻¹⁶ A higher unilateral failure rate of 19-20% on OAE without automated analysis using a 41 dBnHL stimulus has been reported in a special care baby unit population in which the ABR failure rate was similar to that in the present study.¹⁸ Differences between studies in the method of OAE analysis might account for the difference in OAE failure rate: our reliance upon explicit POEMS criteria (see methods) may have improved the specificity. It is also possible that Stevens *et al* tested a proportion of infants before they reached term before transfer to other units, although one would expect this to have been reflected in higher ABR failure rates: in our study almost all babies from the special care baby unit group were tested in the week before discharge to home.

As the aim of neonatal screening is to intervene early to minimise the effect of hearing impairment severe enough to interfere substantially with the development of speech and language, we elected to regard detection of lesser degrees of hearing impairment as 'false positives' in the calculation of specificity and sensitivity. This also avoided contamination of evaluation of the neonatal tests by the inclusion of mild/moderate conductive losses whose incidence rises rapidly in the second six months of life and for which the benefits of intervention are debatable.¹⁹

The higher false positive rate in the group with a family history or craniofacial malformation (fig 2) was not associated with a higher rate of

middle ear dysfunction on neonatal immittance measurement than the other two groups combined (10/51 compared with 60/260). It was, however, associated with a higher incidence of subsequently confirmed *mild* persistent conductive hearing loss (6/61 compared with 4/309) (table). This difference is sufficient to explain the higher false positive rate entirely and these two observations together suggest that neonatal automated OAE are a more sensitive predictor than neonatal immittance of subsequent conductive hearing loss.

Combination of groups of low risk and special care baby unit babies did not conceal a high false positive rate in the special care baby unit group (fig 1). Failure rates in the combined group tend to be marginally higher than for low risk group alone but the upper 95% confidence limit is lower for the combined group than for the low risk group alone because of the larger number of infants in the combined group. The false positive rate in the low risk population is the most influential parameter in determining the test performance for universal screening as this group will be approximately tenfold larger than the special care baby unit group. It seems unlikely that the failure rate in the low risk population was underestimated by adding the special care baby unit group to the low risk group.

In this study automated ABR, although more invasive (requiring application of scalp electrodes) and more time consuming than automated OAE, proved highly specific. This in itself is an important observation but, as with the observations on automated OAE (see below), further study is needed to establish that this technique has the sensitivity of conventional ABR analysis.

The use of a combination of neonatal tests enabled us to derive several screening pass/fail criteria (for example, fail if bilateral failure on automated OAE followed by unilateral failure on automated ABR analysis) which could be relied upon to fail less than 1% of babies irrespective of whether they were nursed in the special care baby unit or the postnatal wards provided there was no craniofacial malformation and no family history of deafness.

SENSITIVITY

All three cases of substantial hearing loss (see methods) that have so far come to light by any method were detected bilaterally on all the neonatal tests. Furthermore, there were indications in the study that automated OAE is also a sensitive test for lesser degrees of hearing impairment: seven of the 10 cases of mild to moderate hearing impairment (all middle ear in type) failed neonatally on automated OAE. Among these 10, three had an abnormal neonatal tympanogram, four failed neonatal ABR, and three passed all neonatal tests (table). In other words, had the aim been to predict subsequent mild to moderate hearing loss, automated OAE would have been the most sensitive neonatal test.

This finding is in agreement with that of Stevens *et al* that 27 out of 29 infants who failed ABR at 53 dBnHL in one ear and 43 dBnHL in

the other on neonatal testing were predicted by failure to produce OAE after presentation of a 41 dBnHL stimulus.¹⁸ In that study neither of the infants failing on ABR and passing OAE testing neonatally was reported to have confirmed *severe* hearing loss on the most recent test: one had ABR thresholds of 30 dBnHL and the other 'still shows an elevated ABR threshold at seven months'.

It is, however, important to stress that, in contrast to the conclusions relating to specificity, the sensitivity of neonatal OAE (or neonatal automated ABR) in detection of hearing impairment has not been reliably determined by the present study nor by any study yet published: because of the small number of severely hearing impaired infants expected in these study populations, a tenfold larger study to calculate sensitivities with the same narrow confidence limits as were derived for specificity is required. Furthermore, a long follow up period to allow any missed impairments to come to light is needed.

PRACTICABILITY

Automated OAE is certainly the most practicable of the neonatal tests used in this study as no scalp electrodes are required. The median testing time for automated OAE of 12 minutes would be substantially reduced in a screening protocol with less comprehensive testing (for example one or two instead of three stimulus intensities). Automated ABR, although a lengthier technique than automated OAE, was quicker than standard ABR testing and also avoided the need for the training and time to evaluate ABR tracings.

POSITIVE PREDICTIVE VALUE

The sensitivity and specificity of a test must be considered in relation to the prevalence of the condition in the population in order to determine the positive predictive value of failing the test: that is the percentage of cases failing the test who will subsequently prove to have an underlying hearing impairment. Several studies, reviewed by Sancho *et al*,² report a prevalence of severe to profound deafness of 2–3/1000 in infancy. Assuming that a neonatal screen of automated OAE followed by automated ABR is indeed 100% sensitive for this condition, one can deduce from the incidence of the condition and from our derivation of a lower 95% confidence limit of the specificity of such a screen of greater than 99% (that is, less than 1% false positives) that the positive predictive value of such a screen could approach 20–30%.

FUTURE STUDIES

Having established the specificity of the neonatal tests, we wish to establish whether a neonatal screening protocol should either replace the 8 month distraction test or be used as an adjunct to it or not be used at all. To this end, we are currently undertaking a feasibility study to determine what staff and equipment would be required to implement effectively a screening

protocol for all newborn babies before discharge from hospital. We plan to follow the feasibility study with a screening study of sufficient size to determine the sensitivity of the method within narrow confidence limits. Haggard correctly suggests that high false positive rates are the main obstacle to credible universal neonatal screening for hearing impairment.²⁰ If we can confirm the high specificity reported here in such a screening study and demonstrate that such a screen is effective in reducing the age at which intervention for severe to profound deafness is begun, the case for widespread introduction of such a screen will be greatly strengthened.

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Neonatal at risk screening and the identification of deafness

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Abstract

From a cohort of 10 686 live births, 322 (3%) were identified as being at risk of a hearing impairment defined as moderate, or worse. These neonates were screened by measurement of auditory brainstem responses. The neonatal at risk screening programme was effective in terms of both yield and cost. The mean age at which hearing aids were fitted was 6 months in the children identified by the neonatal screen. Such a programme is both practicable and useful in a district general hospital. The yield from the neonatal programme was, however, only 43% of the total number of deaf children eventually identified from the cohort. The need to identify more deaf children by a sensitive infant distraction test screening programme remains.

The early identification of deafness is an appropriate objective of child health surveillance programmes.¹ Children with a severe hearing impairment, or worse, should be identified in infancy, and a case can be made for early detection of children with moderate permanent hearing loss.² The methods by which such identification can be achieved are being critically reviewed. The infant distraction test given at 7 months of age has been recommended as a universal screening test,³ and this method used properly can be highly effective in identifying deafness in infancy.⁴ Even when such a test is sensitive, however, the age at which a hearing aid is fitted is often delayed until after the first year of life⁵; many now consider that this is too late. The American Joint Committee on Infant Hearing recommended in 1982 that audiological rehabilitation should begin within the first 6 months of life, and this view has been supported by evidence that indicates that fitting a hearing aid at this age improves development of speech.⁶ The screening of neonates for deafness is now therefore a priority for audiology services in the UK.

Measurement of the auditory brainstem response (ABR) is considered the most sensitive method of assessing the auditory acuity of neonates.⁷ Because the procedure is time consuming, however, only selective screening is feasible. The difficulties of identifying children with handicapping conditions by selective screening have been reported in the UK by the Working Group on Risk Registers.⁸ In the USA the Joint Committee on Infant Hearing recommended the use of a risk factor register for selecting the neonatal cohort that would give the highest yield of children with congenital or early onset deafness.

It has been estimated that it should be possible to detect between 50 and 70% of severely or profoundly deaf neonates from this at risk group.⁹ Most such at risk neonates have been in special care baby units, or have a family history of deafness, or a congenital malformation. Neonatal hearing screening programmes have therefore selected for testing this section of the total birth cohort; it comprises 7-10% of newborn infants.

The validity of such neonatal screening programmes has been reported from academic departments of audiology and from regional (level 3) neonatal intensive care units.¹⁰⁻¹⁴ For such programmes to be useful, however, it must be possible to implement them in districts of different characteristics throughout the country. Most health districts have a special care baby unit (a level 1 or 2 neonatal intensive care unit).

In the present study we evaluated a neonatal hearing screening programme that was introduced in 1987 in the east London health district of Waltham Forest, which has a population of around 250 000. Maternity and paediatric care is provided from Whipps Cross Hospital, the special care of neonates being undertaken by a level 2 neonatal intensive care unit. There is also a diagnostic and rehabilitative paediatric audiology service. The selective neonatal hearing screening programme was implemented as an addition, the infant distraction test being retained as the universal screening test of hearing at the age of 7 months.

The evaluation of a new hearing screening programme requires the measurement of the number of deaf children identified by the programme, its cost, and its effect on the remaining screening tests retained for use at other ages. We report here the results of our evaluation on a cohort born between January 1987 and December 1989.

Subjects and methods

NEONATAL RISK FACTORS FOR DEAFNESS

The American Joint Committee on Infant Hearing At Risk Register was used, with some revisions, to identify those infants at risk for congenital or early onset deafness (table 1). The register was expanded to include those neonates with a gestational age of less than 32 weeks, those who required ventilation for four hours or longer, and those who developed signs of cerebral illness. The American committee recommended the screening of all neonates who had a family history of hearing impairment during childhood. We limited this to include only those neonates who had a family history of permanent deafness in childhood. The medical

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Table 1 Risk factors for congenital or early onset deafness: criteria used by Redbridge and Waltham Forest audiology services

Family history of deafness that required special education or the fitting of a hearing aid in childhood, or of an inherited condition known to be associated with deafness in childhood, even if there is no known deafness in the family

Congenital malformations either of chromosomal, syndromic, or unknown aetiology including craniofacial, branchial arch, and cervical spine dysmorphology; cleft palate; and any malformation of the pinna excluding isolated ear pits and tags

Congenital infections including clinical rubella, cytomegalovirus, toxoplasmosis, herpes, and syphilis; also any maternal history of possible infection in pregnancy even in the absence of neonatal signs

Perinatal illness that required admission to the special care baby unit for one or more of the following reasons:

- (i) Gestation of less than 32 weeks
- (ii) Birth weight of 1250 g or less
- (iii) Apgar score of 3 or less at 5 minutes
- (iv) Cerebral illness (for example, intraventricular haemorrhage, convulsions, or meningitis)
- (v) Apnoea requiring ventilation of four hours or more
- (vi) Jaundice for which exchange transfusion was considered or undertaken
- (vii) Administration of aminoglycoside antibiotic in potentially toxic doses

Postsnatal illness: bacterial meningitis or neurological disease

and nursing staff of the special care baby unit were taught how to use the register for identifying at risk babies within the unit. Additional training in how to identify at risk infants who had not been admitted to the special care baby unit was given to community medical officers, health visitors, and general practitioners.

ENROLMENT IN THE PROGRAMME

Infants who had one or more risk factor were enrolled to the programme. Those who were not admitted to the special care baby unit were examined for risk factors by the health visitor at the new birth visit, and were subsequently re-examined by the community medical officer or general practitioner at the six week health surveillance check. Referrals were also accepted after the paediatric examination of neonates who were born in the maternity unit but not admitted for special care. The audiology service offers an open access policy for parents, and direct parental referrals were accepted into the programme. One person on the special care baby unit was given the responsibility for referring to the programme, but all the staff took part. Babies who were referred to a regional or level 3 unit were enrolled into the programme on their return to the district, irrespective of the results of electrophysiological tests undertaken in the regional unit.

HEARING SCREENING METHOD

The auditory brainstem response was the method that was used to test hearing.¹⁵ Where possible neonates were tested at a postconceptional age of 37 weeks or more and when they were in a stable condition. In the unit babies were tested from the low dependency area before they were discharged. Babies were recalled in one to two weeks by the unit staff if they had been discharged before their hearing had been tested. Referrals from the unit were tested in a quiet room adjacent to the unit. Referrals from other sources were tested in the community based hearing assessment centre.

Babies were tested when they were asleep or

lying still by an experienced audiologist. Standard silver or silver chloride electrodes were attached to the forehead and the ipsilateral and contralateral mastoid, with 'Blue Tak' and Netelast.¹⁶ Using a Medelec MS91 and an ST5 stimulator, an alternatively inverted click stimulus was presented at a rate of 50 pps through a standard TDH39 headphone held against the baby's ear. The analysis time was 10 ms and the filter band width was 200 Hz–2000 Hz. Two repeatable waveforms of 1000 clicks were acquired at 40 dB normal hearing level (nHL) and 60 dBnHL for each ear. If there was no response the intensity of the stimulus was increased to 80 dBnHL.

A clear and repeatable response at 40 dBnHL was judged a 'pass'. The screening test aimed to identify bilateral deafness that was moderate, or worse, and did not aim to identify bilateral deafness that was moderate, or worse, and did not aim to identify unilateral deafness. A response at 40 dBnHL in one ear only was therefore considered to be a 'pass'.

FOLLOW UP OF INFANTS WHO PASSED THE SCREENING TEST

All the infants who passed the screening test were recalled at 7 months from their expected date of delivery for a behavioural test of hearing. Infant distraction testing, otoscopy, and impedance audiometry were carried out by an experienced audiologist who had not taken part in the neonatal screening. Further audiological assessments were arranged as a result of this 7 month assessment and until an accurate audiological assessment had been achieved by behavioural testing. Arrangements to recall all the infants at 3 years of age for pure tone audiometry have been made, but the results of this test on the entire cohort are not yet available. If an infant did not attend the follow up, the results of the health visitor's distraction test were obtained.

ASSESSMENT OF INFANTS WHO FAILED THE SCREENING TEST

Neonates who did not have a clear and repeatable auditory brainstem response at 40 dBnHL in at least one ear were assessed audiological four to six weeks later at the hearing assessment centre. At this appointment electrophysiological testing to threshold was accompanied by impedance audiometry and an assessment of auditory behaviour. Otoscopy and a medical examination was also done. If this examination confirmed moderate, or worse, bilateral hearing loss the infant was immediately referred to the diagnostic and rehabilitation programmes run at the hearing assessment centre. If such a hearing loss was not confirmed, the infant was reviewed at 7 months in the same way as the infants who had initially passed the neonatal screen.

SCREENING OF INFANTS NOT ENROLLED IN THE NEONATAL PROGRAMME

In the absence of risk factors, deafness was identified by checking a list of features of

auditory behaviour and alerting parents to hearing loss, and by the infant distraction test that was undertaken by the health visitors at 7 months. The coverage of this programme within the district has been almost 90%, and a retrospective analysis of deaf children identified within the district during a 16 year period has confirmed that the distraction test screen identified, among the infants tested, 90% of those with previously unrecognised severe deafness, or worse. The sensitivity of the test in infants with moderate deafness who received a distraction test rose to 70% during the early 1980s. The hearing assessment centre received the referrals from the infant distraction test screen, as well as the reactive referrals resulting from professional and parental concerns.

ANALYSIS OF RESULTS

Babies in whom the risk factors did not conform to those specified were accepted for screening, but their data were collected separately. A proportion of the neonates admitted to the district's special care baby unit were from neighbouring districts. If they were enrolled in the neonatal screening programme, they were reviewed in Waltham Forest so that the validity of the neonatal screening test and the yield from the unit could be measured. In assessing the value of the programme within the district, data were restricted to residents of Waltham Forest. Details of all the children with moderate bilateral deafness, or worse, who were identified from the district's three year birth cohort were available from the audiology service's database. Information included the numbers diagnosed, the age at diagnosis of deafness, and the age when the hearing aid was fitted from the different screening programmes and from reactive referrals. The age at diagnosis was defined as the age at which a full audiological assessment confirmed the child's hearing impairment. The clinical and health records were examined to confirm the absence of risk factors in any deaf children who had not been enrolled into the neonatal programme.

Although long term monitoring is continuing, the youngest children in the cohort were born in

December 1989. This is an important limitation of the study. Incomplete ascertainment inevitably biased the mean age at diagnosis and at fitting of the hearing aid of the deaf children identified since the neonatal screening programme. The degree of under ascertainment was estimated by comparing the prevalence of deafness identified from the cohort by the end of the study with the period prevalence of moderate bilateral deafness, or worse, that had previously been reported in children from the district.^{5 17}

Results

In the three year period from January 1987 to December 1989, 12 186 babies were born in the maternity unit at Whipps Cross Hospital. During the same period there were 10 686 live births to residents of Waltham Forest, 796 of whom were not born in the district's maternity unit. Babies referred for neonatal screening totalled 398, but 76 did not conform to the risk factors specified in the register (table 2). Forty eight of these referrals were made during the initial period of the study and consisted of neonates who had been treated with aminoglycosides, but not in potentially toxic doses. This ceased after an early audit, but the remaining 28 were made during the course of the study. Although they were all tested and followed up, none had a hearing impairment and they were excluded from the results of the evaluation.

In all, 322 neonates were admitted to the programme, and 278 were born to residents of Waltham Forest. They represented 2.6% of the live births to residents of the district during the three years. Of the neonates admitted to the programme, 44 (14%) were enrolled from sources other than the special care baby unit (table 3).

The mean gestational age of the babies who were screened was 35 weeks, with a mean chronological age of 6 weeks at the time of the initial test. The outcome is shown in figure 1. Of the 322 babies tested only those 47 (15%) who failed the screen at 40 dBnHL in both ears were referred for diagnostic audiological assessment.

After the diagnostic assessments 12 infants of the 322 screened (4%) were identified as having permanent bilateral deafness which was moderate, or worse, in the better ear. The comparative numbers who had the different risk factors is shown in table 4. Of the 874 babies admitted to the special care baby unit, eight (0.9%) had such a hearing loss, but because less than a third of these infants required a neonatal hearing test, the number was eight of the 278 (3%) from the unit who were enrolled into the programme. Of the six infants whose deafness resulted from perinatal illness, all had at least three perinatal risk factors, and only one was born with a gestational age of more than 32 weeks. Of the 44 infants referred from other sources in only four (9%) was deafness identified by the screening test.

Of the 275 infants who passed the initial screen, 88% (n=243) were re-examined audio-

Table 2 Causes of over-referral for neonatal screening (n=76)

Cause	No (%)
History of aminoglycoside treatment (below toxic dose)	48 (63)
Parental concern	16 (21)
Isolated ear pits or ear tags	7 (9)
Inappropriate family history of deafness	5 (7)

Table 3 Sources of referral correlated with risk factors

	Special care baby unit	Community child health surveillance	Acute paediatric service	Audiology service	Parents
Family history	1	10	7	8	1
Congenital malformations	26	8	1	0	0
Congenital infection	0	0	0	0	0
Perinatal illness	251	7	1	0	0
Postnatal illness	0	0	1	0	0
Total	278	25	10	8	1

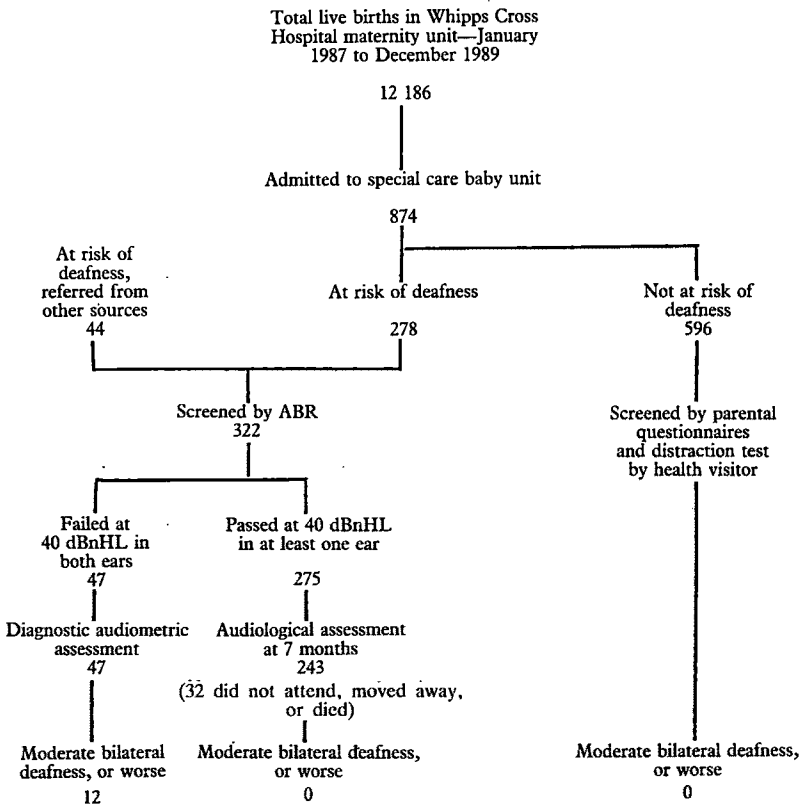


Figure 1 Flow diagram of the neonatal screening programme and outcome.

Table 4 Incidence of deafness correlated with different risk factors

	No screened	No with moderate or bilateral deafness	Incidence of deafness as percentage of No screened
Family history	27	2	7
Congenital malformations	35	4	11
Congenital infection	0	0	0
Perinatal illness	259	6	2
Postnatal illness	1	0	0
Total	322	12	4

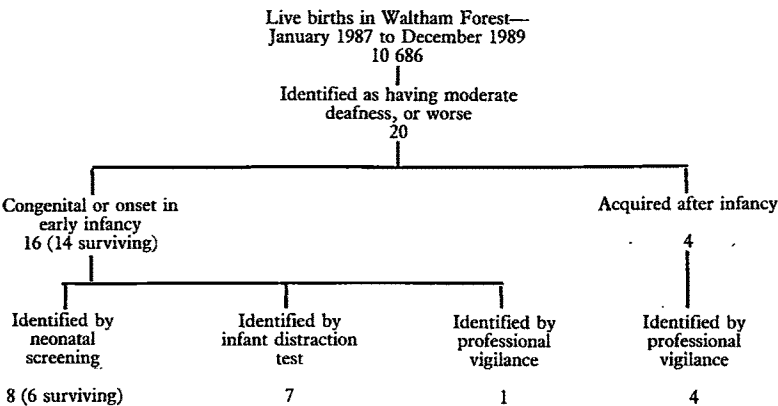


Figure 2 Methods of identification of children with moderate deafness, or worse, who were resident in Waltham Forest and born from January 1987 to December 1989.

Table 5 The mean (range) age at diagnosis and fitting of hearing aid (months)

	No of children with deafness identified	No of children fitted with hearing aid	Age at diagnosis	Age at fitting of hearing aid
Neonatal screening programme	6	5	2 (0.5-5)	5.7 (1.5-8)
Infant distraction programme or vigilance	8	7	12.5 (9-30)*	16 (11-34)

*The range is wide because a child was included who was identified in infancy and then went abroad; the diagnosis was not confirmed until his return.

logically at 7 months. None had moderate deafness, or worse, bilaterally, confirming that the ABR test was 100% sensitive. The test had a specificity of 89%.

The hearing of the infants was not, however, readily measured at the 7 month examination; 134 of the 322 infants who had received a neonatal hearing test (42%) were not readily testable by the distraction test at a corrected age of 7 months. Of these, all but 13 were successfully tested later in infancy when their auditory behaviour had matured. These 13 children had either an additional physical handicap or developmental retardation such that audiological assessment by behavioural methods was difficult, even for an experienced audiologist. The measures of validity of the neonatal screening test were therefore only completed after almost half the infants had been audiological re-examined on more than one occasion. A few required multiple re-examinations. Of the 12 infants who were identified as by the neonatal screen being permanently deaf, two died later in infancy, and five had an additional handicap. In the remaining five, however, deafness was the only appreciable impairment.

The effectiveness of the neonatal screening programme within Waltham Forest was assessed. During the three year period of the study there were 10 686 live births to residents of the district. A total of 20 children with a moderate hearing loss, or worse, in the better ear have been identified from this cohort by hearing screening programmes or by professional and parental vigilance (fig 2). Two of the children died in infancy. The prevalence of this degree of deafness within the cohort was therefore 1.7/1000 compared with the previously reported prevalence of 1.9/1000. There was slight under ascertainment during the period of the study and examination of the degree of hearing loss identified in children in the cohort suggested that two children with moderate deafness had not been identified by the end of the study.

The routes through which the children with this degree of deafness were identified are shown in fig 2. Of the 14 surviving children with deafness in infancy, six (43%) were identified from the 278 who underwent neonatal screening. The eight children who were subsequently identified had not been considered to be at risk of deafness during the neonatal period. A retrospective examination suggested that three of these eight were at risk. One had congenital rubella, but the history was obscure and there were no other physical signs. The two others had a dominantly inherited deafness, but in both cases the family history was not known until after audiological examination of other members of the family; initial direct question-

ing had not uncovered the presence of deafness within the family. None could have reasonably been identified by the use of the at risk register.

The mean age at diagnosis of the deafness was calculated for those children identified from the different screening programmes (table 5). Two of the children had not been fitted with hearing aids by the conclusion of the study. In both cases the parents initially did not accept the need for the child to wear a hearing aid, although in both cases the presence of the deafness was acknowledged and follow up arrangements had been made.

The mean age at diagnosis for those identified by the neonatal screen was significantly lower than for those identified either by the infant distraction test screen or by vigilance ($t=4.01$, $df=12$, $p<0.01$). Consequently the mean age at which hearing aids were fitted for the children identified by at risk screening was significantly reduced ($t=2.87$, $df=10$, $p<0.02$).

Discussion

The results of the study confirmed the sensitivity of the ABR with a lower stimulus intensity of 40 dBnHL for identifying from the neonates tested those who had moderate deafness, or worse. From the three year cohort, six of the 14 surviving children with this degree of deafness present in infancy (43%), were identified by the neonatal screening of those with risk factors.

The selection of the neonates at risk who required screening was highly effective. By selecting and screening 278 neonates from a birth cohort of over 10 000, 43% of the deaf children were identified. Of the eight deaf infants who were identified subsequently, seven were identified by the infant distraction screening programme, and one by professional vigilance. To identify the seven children by distraction testing, however, over 9000 children were screened within the district.

The effectiveness of the neonatal screening programme resulted from successfully identifying those neonates with risk factors for congenital or early onset deafness. It has previously been recommended that all admissions for special care should be screened. As in other districts this was 7% of the hospital births. By selecting only those neonates with specific risk factors from within the level 2 unit, however, only a third of the admissions to the special care unit received a hearing test.

If all babies discharged from the unit had been screened, the number diagnosed would not have increased. Although the largest number was obtained from the special care baby unit, the screening of those neonates referred from other sources was the most efficient. As a percentage of those screened, the number was more than three times greater among those referred from other sources. The highest yield as a percentage of those screened was among those neonates referred with a congenital malformation, or with a family history of deafness. The community child health service played an important part in referring such infants, and if such a programme is to be effective the community child health professionals must continue

to refer at risk neonates. If general practitioners are to make a contribution, further education within the district is required.

Not all deaf children who are at risk can be identified from a neonatal risk factor register. Of the eight deaf infants who were not referred for neonatal screening, a retrospective examination of the causes of their deafness confirmed that three of them were at risk. Using a wider set of risk factors would not have identified them, however, and they could not have reasonably been identified as being at risk within the neonatal period. This discrepancy may explain why some authors have suggested that a higher proportion of deaf infants are identifiable from an at risk register⁹; in reality not all these infants will be identified neonatally.

The efficiency of the neonatal screen was reflected in the cost/hearing impairment detected. The ABR screening and the diagnostic testing of those who failed the screen were done by an audiological scientist during a weekly session in the special care baby unit and a fortnightly session in the community hearing assessment centre. With four neonatal screenings, or two diagnostic ABRs being done during each session, the programme was sustainable, even allowing for periods of absence. Taking account of the costs to the health authority of employing an audiological scientist for these sessions, but excluding equipment costs and other overheads, the cost of identifying a hearing impairment in a child by the neonatal screening programme was just under £1250. Currently (1991) the same cost would be incurred by employing a grade A scientist, or an audiology technician at senior grade (MTO 3), to undertake the ABR testing. This is less than the national cost of £4000 suggested by the Institute of Hearing Research in Nottingham. The Nottingham programme provides ABR screening for neonates admitted to level 3 units and employs a fulltime nurse (G grade) to undertake the testing (A Davis, Institute of Hearing Research, Nottingham, personal communication). In most districts, by successfully identifying those neonates with risk factors from within a level 1 or 2 unit, most neonates admitted for special care will not require screening, and a beneficial yield can be obtained at lower cost.

The assessment of hearing by behavioural methods was difficult in many of the infants at risk, and half the deaf children identified by the neonatal screen had additional physical handicaps that would have delayed the introduction of audiological rehabilitation if their deafness had been identified solely on behavioural assessment. An early failure on ABR screening assisted in the diagnosis of deafness in these children, and hearing aids were fitted to the children identified by neonatal screening at a mean age of 6 months. The mean age of fitting hearing aids to the children who were subsequently identified was 16 months, and because of the lack of long term monitoring of the cohort, not all the children with moderate bilateral deafness, or worse, will have yet been identified. Their later identification will further increase the mean age at which deafness is

confirmed in those not identified by the neonatal at risk screening programme.

The introduction of the neonatal hearing screen has therefore been of value to the district. Within districts with similar characteristics the implementation of such a programme can successfully identify just under half of the children with congenital or early onset deafness, and is relatively cost effective. Most deaf children, however, must still be identified by the traditional hearing screening programmes, or by sensitive parental and professional observation.

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Impact of sleep and movement on gastro-oesophageal reflux in healthy, newborn infants

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Abstract

Seventy four normal, healthy newborn babies were studied to examine the relationship between gastro-oesophageal reflux, sleep state, and movement. Multichannel pen recordings were made to determine sleep state, movement, breathing, and reflux. The mean number of reflux episodes per hour was highest in wakefulness, followed by active and indeterminate sleep. In quiet sleep reflux rarely occurred. The mean duration of reflux episodes per hour was longest in active sleep followed by wakefulness, indeterminate and quiet sleep. There was a strong positive correlation between duration of reflux and movement time for wakefulness, active and indeterminate sleep. Movement preceded 88% of all reflux episodes.

Physiological reflux occurs in most newborn infants but is clinically inapparent. The results suggest that state and movement are related to the incidence and duration of reflux. Sleep state is therefore an important variable in determining normal values for reflux in infancy since developmentally the amount of sleep time lessens but quiet sleep proportionally increases.

Gastro-oesophageal reflux is a well known clinical problem in both term and preterm infants. Despite this, there is relatively little information about physiological reflux in the sleeping neonate.

Some information is available for control infants, but this is often deficient in important variables, such as adequate numbers of infants studied at a particular age and the selection criteria. This grouping of data over a wide age range in infancy may ignore developmental changes, while selection of infants from a neonatal special care nursery rather than a healthy, asymptomatic population, may introduce confounding variables to the analysis. The position of both the infant and the pH probe, and the type of milk, are additional variables for which methodological details are frequently incomplete.

Only two studies have examined a large number of neonates. Vandenplas and Sacre-Smits described normal values for reflux from 24 hour pH recording in 92 bottle fed neonates, aged 5-15 days. However, the method of selection and prior health of these infants were not stated.¹ Gouyon *et al* selected 46 control infants from a neonatal unit, 50% of whom were preterm. They were studied at a postnatal age of 2-21 weeks.² The possible impact of develop-

mental changes, however, were not taken into account.

Another variable that has not been adequately explored is sleep state. As young infants spend the major part of the day asleep, this is potentially relevant. Previous studies of sudden infant death, and of those who have had a 'near miss' have suggested that the state of wakefulness or sleep may be important in determining the number of reflux episodes.³⁻⁵

An additional measure that may highlight different underlying mechanisms for reflux is whether or not movement precedes reflux. In older infants, defined as symptomatic controls (with symptoms thought to be related to reflux but with a pH <4.0 for <6% of total monitored time), movement frequently preceded reflux events during sleep (85%). In subjects with pathological reflux (a pH of <4.0 for >6% of total monitored time), movement preceded reflux in only 36% of the events.⁶ While Sondheimer did not describe the mechanisms for these reflux events, others have noted that most asymptomatic reflux in healthy infants is synchronous with swallowing and associated with reflex opening of the lower oesophageal sphincter, which is usually prolonged. By contrast, symptomatic reflux, especially if associated with oesophagitis, is asynchronous with swallowing and usually due to transient relaxation of the lower oesophageal sphincter.^{7,8}

To examine the possible influence of sleep and movement on reflux, variables known to influence the incidence of gastro-oesophageal reflux were controlled. Subjects were then randomly selected from a normal, healthy population of newborn term infants. The aim of the study specifically was to examine the relationship between wakefulness, sleep state, and physiological reflux. The relationship between movement and both the onset and the duration of reflux was also explored.

Methods

SUBJECTS AND SELECTION

Seventy four healthy term infants from the public maternity ward at King George V Hospital were studied between June 1989 and June 1990. The ethics committee of King George V Hospital approved the experimental protocol.

During this 12 month period, 1988 babies were born to mothers in the public ward of the hospital. Estimates from a one month sample period suggested that a total of 454 (23%) babies met the entry criteria, but only 200 infants could be studied (one per day) in the available

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time. Permission was sought from 104 mothers of whom 13 refused. Verbal informed consent was obtained from 91 randomly selected mothers. However, 17 of these studies were unsuccessful due to either limited sleeping or technical difficulties.

Entry criteria required that the infants were: born to English speaking mothers who had no complications of pregnancy, such as drug and alcohol abuse, hypertensive disease of pregnancy and diabetes; at a gestational age of 37–42 weeks; size appropriate for gestational age; not asphyxiated at birth; not treated for jaundice; aged 2–8 days if formula fed and 3–8 days if breast fed, to ensure a milk supply.

Of the 74 babies in the final sample, 38 were girls and 36 boys. There were 37 breast and 37 formula fed babies, each being fed until satisfied. Fifteen infants received S-26 formula (Wyeth) and 22 infants Nan formula (Nestlé). The feeds ranged in volume from 15 to 115 ml, the mean (SD) were 57 (23) ml.

POLYGRAPHIC RECORDING OF SLEEP STATE

Multichannel pen recordings were made while the infants were lying supine, in a quiet, warm room for four hours after their morning milk feeds. To determine sleep state, electrodes for recording an electroencephalogram (EEG), electrooculogram (EOG), and submental electromyogram (EMG) were used (EOG and EMG electrodes were only used for the first 20 infants). In the subsequent 54 cases, EOG and EMG electrodes were replaced by piezoelectric transducers, one being positioned on the upper eyelid and one on the laryngeal prominence. As a movement detector, the piezoelectric transducer produced a better signal to noise ratio.

Breathing was recorded by abdominal pneumogram and by nasal flow of end tidal carbon dioxide. The breathing pattern was used to assist in defining sleep state.

MEASUREMENT OF GASTRO-OESOPHAGEAL REFLUX

A pH microelectrode (M1508, Microelectrode Inc, 1.2 mm outer diameter) was introduced nasally in all but two infants, when it was placed orally. It was positioned 6 cm above the lower oesophageal sphincter, according to Strobel's formula, which relates body length to oesophageal length.⁹ A reference electrode (B140249, Beckman Instruments Inc, used on 54 babies and MI402, Microelectrode Inc, used on 20 babies) was attached securely to the infant's leg. The electrodes were connected to a pH meter (Activon, Model 209) through a patient isolation unit and the pH recorded at a paper speed of 100 mm/minute. At the beginning and end of each study, the pH recording system was calibrated in buffers of pH 4 and 7. Recordings were excluded if a calibration drift of 0.3 units occurred after the test. Gastro-oesophageal reflux was defined as a decrease in pH by at least one unit to pH less than 4 for 15 seconds or longer.

ANALYSIS OF RECORDINGS

EEG, EMG, EOG, breathing and oesophageal

pH were recorded continuously on an eight channel pen recorder (Model 78D, Grass Instruments Co). Behavioural observations regarding sleep/wake state and body movement were also recorded continuously on the polygraph paper.

The record was divided into successive epochs of three minutes each by one observer using the method described by Anders *et al.*¹⁰ This defined the sleep state and occurrence of arousal. States were scored as either awake, active, quiet, or indeterminate sleep. If a state occurred for more than half of the three minute epoch, it was considered that this particular state was present.

ANALYSIS OF GASTRO-OESOPHAGEAL REFLUX

The third and fourth postprandial hours were chosen for analysis. This allowed time for the stomach contents to become acidic so that acid reflux could be detected by the pH probe. In addition, differences in milk volume were unlikely to have an effect on reflux frequency more than two hours after feeding.¹¹ To confirm this, the volume of bottle milk feeds was measured and related to both the number and duration of reflux episodes.

A minimum of 90 minutes' recording time was required for analysis. If no reflux was recorded at the end of a study, a gastric pH of <4 was confirmed by advancing the pH electrode beyond the calculated oesophageal length.

The recording was analysed in each state for the following: (1) number of reflux episodes; (2) duration of reflux episodes; (3) number of reflux episodes lasting more than five minutes; and (4) movement time preceding and during each reflux episode. Movement was defined by deflection of the submental EMG or piezoelectrode positioned over the larynx. This detected not only swallowing and sucking but also gross body movements which were also confirmed by interference on other analogue signals. Behavioural observations were also scored on the polygraph paper.

STATISTICAL ANALYSIS

The mean and 95% confidence intervals were generated for all reflux parameters in each state. Regression analysis was performed on duration of movement versus duration of reflux. Correlation coefficients were determined for each sleep state.

Results

SUBJECTS

The mean (SD) for gestational age, birth weight, and postnatal age of the 74 infants studied were 39 (1) weeks, 3436 (472) g, and 4 (1) days respectively.

POLYGRAPHIC SLEEP RECORDING

Figure 1 shows typical recordings for quiet sleep and active sleep. The amount of time spent in each state varied considerably. Over the total study period 12% of time was spent in

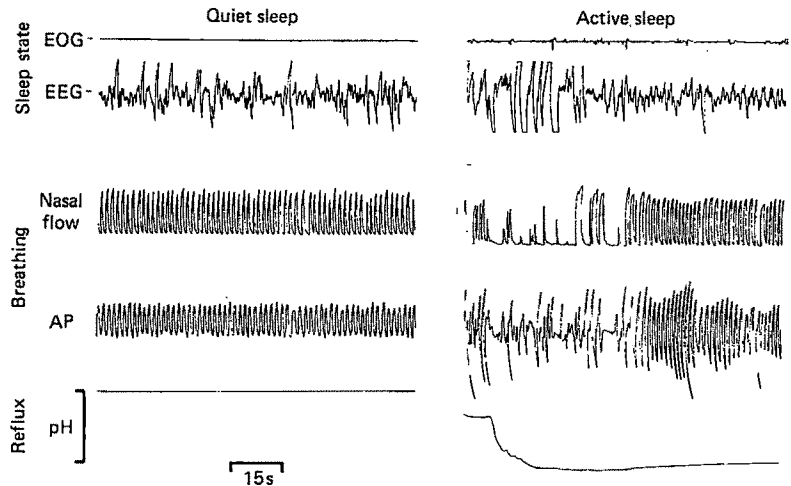


Figure 1 Typical polygraphic trace in quiet and active sleep showing a stable pH usually between 5 and 7, during quiet sleep. A reflux episode is shown in active sleep with a sudden decrease in pH, accompanied by transient body movement, reflected by the movement artifact on the EEG trace. AP, abdominal pneumogram.

wakefulness, 53% in active sleep, 14% in indeterminate sleep, and 21% in quiet sleep.

GASTRO-OESOPHAGEAL REFLUX

A total of 227 episodes of reflux were recorded by the pH meter in the 74 infants. Only 13 of these episodes were clinically apparent.

Fifty six of the 74 infants studied (76%) demonstrated at least one reflux episode during the third and fourth postprandial hours: 52 (70%) had one or more reflux episodes in the active sleep state, 11 (15%) demonstrated reflux in indeterminate sleep, while three babies (4%) had a total of five episodes in quiet sleep.

The mean number of reflux episodes per hour was highest in wakefulness, followed by active sleep, and then indeterminate sleep. Reflux was a rare occurrence in quiet sleep (table). Although more reflux episodes per hour occurred in wakefulness, reflux was most prolonged during active sleep, followed by wakefulness, indeterminate and quiet sleep. The same trend was observed for the mean number of reflux episodes lasting five minutes or more per hour (table).

In all states there was a positive correlation between the duration of reflux and the duration of movement. Figure 2 shows the regression line for duration of reflux versus duration of movement for active sleep. The correlation coefficients were 0.88, 0.84, 0.86, and for wakefulness, active sleep, and indeterminate sleep respectively. Movement preceded 88% of all reflux episodes.

The volume of the milk feed was unrelated to either the number or duration of reflux episodes

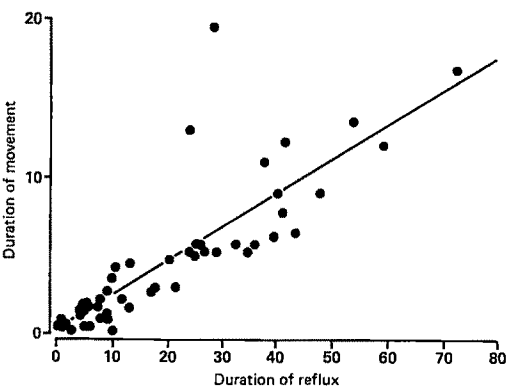


Figure 2 Regression line for duration of reflux (minutes) versus the duration of movement time (minutes) in active sleep. The correlation coefficient is 0.84.

during the third and fourth postprandial hours. The amount of milk consumed/kg of body weight/day (ml/kg/day) was calculated for the 37 infants who were fed formula milk. Correlation coefficients for milk consumed versus episodes and duration of gastro-oesophageal reflux were not significant, being 0.16 and 0.18 respectively.

Discussion

This study provides new information on the frequency and duration of reflux during sleep and wakefulness in healthy newborn infants at term, after normal pregnancies. These data confirm a relationship between gastro-oesophageal reflux, sleep state, and movement.

During sleep, both the occurrence and duration of reflux was most frequent in the active sleep state: 70% of babies demonstrated reflux in this sleep state. By contrast, reflux in quiet sleep was very uncommon. The pH trace in quiet sleep was characteristically stable and usually between pH 5 and 7.

This difference in state related reflux events has been observed for other physiological variables such as respiratory reflexes in the newborn. For example, the ventilatory response to hypoxaemia,¹² the inhibition of intercostal muscles leading to paradoxical movement of the rib cage,¹³ and the laryngeal response to stimulation in the adult dog,¹⁴ differ greatly depending on the state of active or quiet sleep. It has been proposed that different neural pathways operate in the various sleep states.¹⁵

Some indirect evidence supports this concept with regard to reflux. Primary peristalsis, which is initiated by swallowing, and increased gastric pressure secondary to movement are two common mechanisms associated with reflux in healthy infants.⁸ In this study movement commonly preceded reflux (88%) in the awake state

Results as mean (95% confidence intervals) for gastro-oesophageal reflux episodes in all states of sleep and wakefulness

	Wakefulness	Active sleep	Indeterminate sleep	Quiet sleep
State time (min/hour)	7:00 (5:34 to 8:66)	32:00 (30:00 to 34:00)	8:50 (7:43 to 9:57)	12:50 (10:97 to 14:03)
Episodes/hour	2.65 (1.56 to 3.74)	1.87 (1.45 to 2.29)	0.77 (0.17 to 1.37)	0.22 (-0.03 to 0.47)
Duration (min/hour)	8:40 (5:20 to 11:60)	12:10 (9:04 to 15:16)	7:55 (4:18 to 10:92)	5:25 (2:13 to 8:37)
No of episodes >5 min/hour	0.54 (0.16 to 0.92)	0.90 (0.63 to 1.17)	0.37 (0.11 to 0.63)	0.30 (0.07 to 0.50)

and during active and indeterminate sleep. Although swallowing was not recorded, swallowing,¹⁶ peristaltic activity,¹⁷ and movement are uncommon in quiet sleep as opposed to active sleep. The rare occurrence of reflux in quiet sleep is consistent with these observations. It may suggest that neural pathways that underlie programmed swallowing do not operate in quiet sleep.

In infancy, increasing time is spent in quiet sleep with advancing age, the average being 24% in the first week, 44% at 3 months, and 50% at 6 months.¹⁸ The values for active sleep are 58%, 42%, and 34% respectively. Physiological reflux in sleep is therefore likely to be less frequent with increasing age during infancy. The striking difference in state related reflux in this study suggests that the total duration of active sleep during pH monitoring is an important variable in calculating the frequency and duration of reflux in infants.

The extent to which reflux occurs and is unrecognised in the newborn was reflected in the few clinically evident refluxes. Thirteen of the 227 refluxes were clinically apparent as milk in the mouth or nares. Thus conclusions as to possible effects of reflux on heart rate, breathing, and aspiration are valid only with continuous pH monitoring. The difficulty in interpreting any effect of reflux on these events, however, is complicated by the observation that movement and reflux are closely related. Movement itself frequently interferes with the usual analogue recordings of heart rate and breathing. This observation, that body movement is correlated with the duration of reflux, has not been previously published. However, both Ariagno *et al* and Paton *et al* have observed that reflux is frequently preceded by movement in older infants presenting with either acute life threatening episodes or significant reflux.^{19, 20} The reason as to why the duration of body movement is correlated with the duration of reflux in all states is unclear. Other physiological recordings of EEG, EOG, and EMG did not suggest this represented arousal when the infant was in active sleep. Whether body movement represents a stimulus or a response to reflux might be aided by oesophageal manometry.

An attempt was made to control the known variables which influence both the rate and duration of reflux. The results indicate a wide intersubject variance of reflux in healthy, newborn infants. Recent studies in healthy adults,²¹ and adults and children,²² with symptomatic reflux also indicate a large intrasubject variance with 24 hour pH recordings.

In conclusion, these data indicate that physiological gastro-oesophageal reflux is a common but not usually evident event in both wakeful-

ness and sleep in healthy, newborn infants. Both the occurrence and duration of reflux appears to be related to sleep state and movement.

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Patient triggered ventilation using a flow triggered system

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Abstract

The role of patient triggered ventilation (PTV) for the newborn was assessed using a new patient triggered ventilator, the Draeger Babylog 8000, which incorporates significant improvements in both ventilator performance and the triggering system. Thirty three infants, median gestational age 30 weeks and postnatal age 2.5 days, were entered into the study to compare blood gases obtained during conventional and patient triggered ventilation. Oxygenation did not improve with PTV in the group overall but increased significantly (median change 7%) in infants greater than 28 weeks' gestation. Arterial carbon dioxide tension (P_{aCO_2}) decreased during PTV in the majority of infants (median reduction 7%), this was not related to the gestational or postnatal age, but was greatest in infants previously on a low conventional ventilation rate. Blood gases (both P_{aO_2} and P_{aCO_2}) deteriorated in infants requiring the highest inspired oxygen concentration. We conclude that patient triggered ventilation is most useful in infants with mild respiratory distress.

Patient triggered ventilation (PTV) was reintroduced as a method of respiratory support for neonates in 1986.¹ Since that time there have been a series of studies which have assessed both the possible short¹⁻³ and long term benefits of PTV.⁴⁻⁵ In the majority of infants oxygenation acutely improves on transfer from conventional ventilation to PTV¹⁻³ but PTV fails to provide a successful method of respiratory support in infants of less than 28 weeks' gestation⁴ or if it is started in the first 24 hours of life.⁵ A predictor of failure of PTV was an asynchronous respiratory interaction, with inflation occurring either late in inspiration or even in expiration, as a result of a long trigger delay.⁵ All these studies have employed a modified conventional neonatal ventilator (model HV 2000, SLE) with a variety of triggering systems.

Recently, purpose built patient triggering ventilators have appeared. We have demonstrated that one such ventilator (Draeger Babylog 8000) has a performance superior to the SLE, with a much shorter trigger delay: a median of 80-100 ms (Draeger) compared with a median of 200-250 ms (SLE).⁶ The Draeger Babylog 8000 also has the advantage of no inadvertent positive end expiratory pressure (PEEP) at high flow rates⁷ or the fast ventilator rates which are frequently triggered by very immature infants.⁸ Thus it seems likely that this

ventilator could be used with success in a more varied group of infants. Our aim, therefore, was to use the Draeger ventilator to redefine the optimal role of PTV.

Methods

Infants were entered into the study when they had been stable on conventional ventilation for at least two hours and when a ventilator became available. All infants had previously been ventilated using Sechrist ventilators and had blood gases within the clinically acceptable range (pH 7.25-7.4, arterial oxygen tension (P_{aO_2}) 5.33-9.33 kPa, arterial carbon dioxide tension (P_{aCO_2}) 4.67-6.67 kPa).

The patients were then changed over to the Draeger Babylog 8000 ventilator and ventilated conventionally for one hour at the same settings as were previously in use. The ventilator was then switched into patient triggered mode for at least one hour. The Draeger Babylog 8000 utilises an airflow triggering system, a hot wire anemometer, which has the advantage of not increasing the dead space of the patient circuit. We have demonstrated that the median trigger delay of this system is between 80 and 100 ms at inflation times between 0.24 and 0.4 seconds.⁶ On switching into the patient triggered mode the peak inspiratory pressure, PEEP, gas flow rate, and inspired oxygen concentration were not changed. An inflation time initially of 0.4 seconds was used, reducing in steps of 0.02 seconds, if necessary, until the spontaneous respiratory effort was no longer visibly distinct from the positive pressure inflation.

Throughout the study infants were monitored continuously using a Searle intra-arterial electrode or transcutaneous oxygen electrode. Infants were withdrawn from the study if, during PTV, their continuous monitoring demonstrated that the P_{aO_2} was below 5.33 kPa. Arterial blood gas samples were obtained from the indwelling arterial line one hour after changing to the Draeger ventilator used conventionally and then again after one hour of trigger ventilation.

ANALYSIS

Differences in P_{aCO_2} and P_{aO_2} between study periods were assessed for significance using a paired Wilcoxon rank sum test. The change in P_{aO_2} and P_{aCO_2} over the first hour of PTV was expressed as a percentage of the values obtained immediately before PTV; these were then related to the infant's gestational and postnatal age and the severity of the infant's respiratory

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disease. Relationships were assessed for significance using a Wilcoxon rank sum test or Fisher's exact test.

Patients

Thirty three infants, all less than 35 weeks' gestational age, were recruited into the study. Their median (range) birth weight was 1508 (592-2700) g and gestational age 30 (24-34) weeks; they were studied at a median (range) postnatal age of 2.5 (0.25-50) days. The infants were all ventilated because of respiratory distress associated with prematurity. Immediately before the study their median (range) ventilator rate was 25 (4-90) breath/minute, peak (range) inspiratory pressure 17 (12-25) cmH₂O and inspired oxygen concentration 35 (21-80)%.

Ethical permission for this study was granted by the King's College Hospital ethics committee.

Results

No infant had to be withdrawn from the study because of low oxygen concentrations demonstrated by continuous monitoring. On analysis of the arterial blood gas concentrations at one hour, however, one infant (26 weeks' gestation)

had a PaO₂ of 4.80 kPa, although her continuous monitoring had suggested her oxygenation to be at the higher level of 5.33 kPa.

No significant change was found in PaO₂ when blood gases were compared between the period of conventional ventilation and PTV: PaO₂ increased in 17 patients, decreased in 13 and there was no change in the remaining three infants (fig 1). Oxygenation significantly improved in infants greater than 28 weeks' gestational age ($p<0.05$), with a median (range) improvement in PaO₂ of 7 (-28 to +42)%. Fifteen of the 23 infants of gestational age greater than 28 weeks had an improvement in oxygenation, compared with only two of the 10 infants less than 28 weeks gestational age ($p<0.05$). Oxygenation also significantly improved in the subgroup of infants of greater than 28 weeks' gestation who were ventilated at a rate of more than 15 breaths/minute ($p<0.05$). There were no significant relationships between changes in oxygenation and postnatal age, fractional inspired oxygen concentration (FIO₂) or peak inspiratory pressure (table 1).

Paco₂ showed a significant decrease over the PTV study period, decreasing in 21 patients and increasing in 12 patients, median (range) change -7 (-43 to +29.4)% ($p<0.05$). This change in Paco₂ was neither significantly related to gestational nor postnatal age (fig 1). In the 12 patients whose Paco₂ increased, the median ventilator rate on conventional ventilation was significantly higher than in the 21 patients in whom Paco₂ decreased ($p<0.05$) (fig 2, table 2). No significant relationships were found between changes in Paco₂ and either the peak inspiratory pressure or improved oxygen concentration (FIO₂) (table 2).

The improvement in oxygenation was associated with a reduction in Paco₂ in 12 patients, but a rise in Paco₂ in five others. These five infants had been previously ventilated at a significantly higher rate than the rest of the study group ($p<0.05$). A deterioration in PaO₂ was accompanied by a fall in Paco₂ in nine patients (these infants were significantly less mature, but older than the rest of the study group; $p<0.05$) and a rise in Paco₂ in seven others. Infants in whom there was no improvement in either PaO₂ or Paco₂ required a higher inspired oxygen concentration ($p=0.054$) and peak inflating pressure than the remaining infants (table 3). Infants whose blood gases improved on PTV were maintained on this mode for up to several days or until extubation; no complications were experienced.

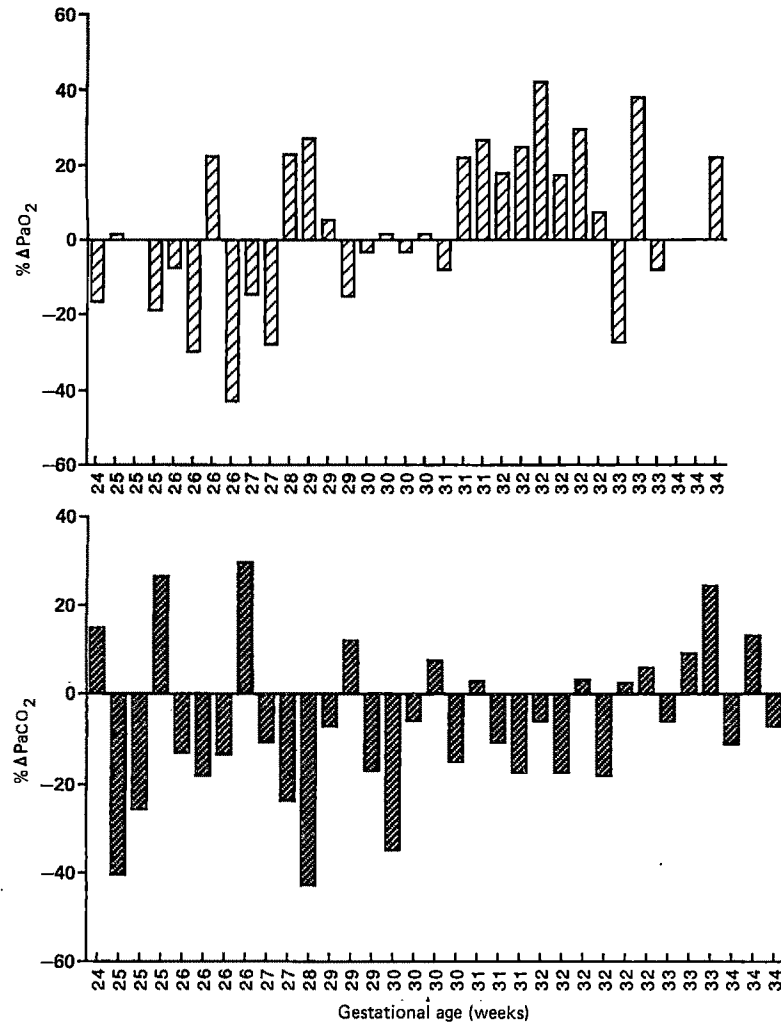


Figure 1 Percentage change in PaO₂ and Paco₂ during PTV related to gestational age. Individual patient data is demonstrated by separate bars.

Table 1 Changes in oxygenation. Results are median (range)

	Increase in PaO ₂	No change or decrease in PaO ₂
No of infants	17	16
Ventilator rate during conventional ventilation (breaths/min)	30 (7-90)	24 (4-78)
FIO ₂ (%)	30 (21-70)	35 (21-80)
Peak inspiratory pressure (cmH ₂ O)	17 (12-22)	15 (12-25)
Postnatal age (days)	2 (0.25-46)	2.5 (0.25-50)

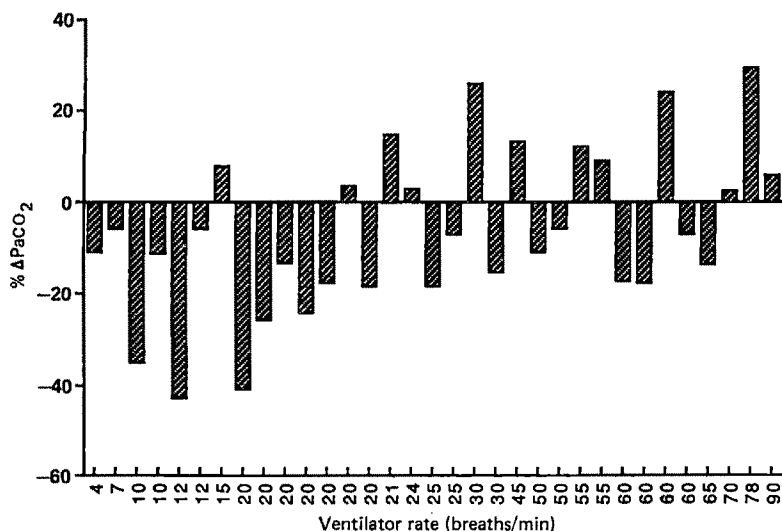


Figure 2 Percentage change in PaCO_2 related to ventilator rate during conventional ventilation.

Table 2 Changes in PaCO_2 . Results are median (range)

	Increase in PaCO_2	Decrease in PaCO_2
No of infants	12	21
Ventilator rate during conventional ventilation (breaths/min)	55 (15–90)	20 (4–65)
FIO_2 (%)	35 (21–80)	30 (21–70)
Peak inspiratory pressure (cmH_2O)	16 (12–25)	17 (12–22)
Postnatal age (days)	2 (0.25–50)	2.5 (0.25–46)

Table 3 Relationships of the changes in blood gases. Results are median (range)

	Increase in PaO_2		Decrease in PaO_2	
	Decreased PaCO_2	Increased PaCO_2	Decreased PaCO_2	Increased PaCO_2
Gestational age (weeks)	31 (25–34)	32 (0.25–4)	27 (25–34)	30 (24–30)
Postnatal age (days)	2 (0.25–46)	3 (0.25–4)	6 (1–37)	2 (0.25–50)
Ventilator rate before PTV (breaths/min)	25 (7–65)	55 (20–90)	20 (4–60)	30 (15–78)
Peak inspiratory pressure (cmH_2O)	17 (12–22)	16 (14–18)	15 (12–18)	18 (12–25)
FIO_2 (%)	30 (21–70)	30 (25–35)	30 (21–50)	50 (21–80)

Discussion

Initial inspection of the results might suggest that PTV appeared to confer no advantage in improving oxygenation over conventional ventilation, as there was no significant improvement in the study population overall. Oxygenation, however, improved in infants of gestational age of more than 28 weeks, with a similar improvement in the subset of that group ventilated at rates of more than 15 breaths/minute. There was a deterioration in oxygenation in the group of infants of gestational age 28 weeks or less, which confirms our preliminary findings in five other immature infants.⁶ Thus, despite using a superior ventilator design and performance,⁶ PTV is still unsuitable for infants of extreme prematurity.

In contrast, changes in PaCO_2 were not significantly related to gestational age. During PTV, tidal volume and minute volume are increased

when compared with similar pressure settings on conventional ventilation.⁹ This improvement in alveolar ventilation on PTV compared with conventional ventilation is particularly likely with the short inflation times⁹ used in this study for infants of all gestational ages. Thus, it is not unexpected that changes in PaCO_2 were not related to the maturity of the infant. Oxygenation, however, is determined by mean airway pressure (MAP).¹⁰ Inflation time during PTV was always shorter than conventional ventilation, particularly in the smallest infants; this would reduce MAP and hence oxygenation.

The only significant relationship of change in PaCO_2 was with the ventilator rate previously used on conventional ventilation. At low rates during conventional ventilation only a small proportion of spontaneous breaths can be supported by a positive pressure inflation. In contrast, during PTV, all spontaneous breaths may trigger the ventilator, resulting in both an increase in tidal and minute volume. Thus PaCO_2 will be affected to a greater extent by changing to PTV from conventional ventilation at a low ventilator rate than a high one. The greater reduction in PaCO_2 at lower ventilator rates suggests PTV may have a useful role in weaning when infants are recovering from respiratory distress syndrome and are usually supported on intermittent mandatory ventilation.

We have previously demonstrated that failure of oxygenation to improve after one hour is an accurate predictor of a lack of successful respiratory support by PTV.^{4,5} The results of this study, therefore, indicate that despite improvements in ventilator design and performance there remains a substantial proportion of infants for whom PTV is not a useful alternative to conventional ventilation. The failure to improve oxygenation in the most immature infants, the greater reduction in PaCO_2 at previously low ventilator rates and the combination of failure of oxygenation and increase in PaCO_2 in infants at the highest inspired oxygen concentration all suggest PTV is more suitable for infants with mild, not severe, respiratory distress.

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Cardiac anomalies complicating congenital contractural arachnodactyly

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Abstract

A newborn boy with congenital contractural arachnodactyly (CCA) was found to have an atrial septal defect, ventricular septal defect, patent ductus arteriosus, and aortic arch anomalies. These resulted in congestive failure but subsequent progressive dilatation of both great arteries and development of aortic regurgitation were associated with eventual cardiorespiratory failure and death at 11.5 months. Others have noted that cardiac anomalies in CCA may be comparable with those of infantile Marfan's syndrome. Our case further extends the spectrum of cardiac abnormalities in CCA and substantiates that there is overlap with infantile Marfan's syndrome. This fact and our literature review suggest that early and complete cardiac assessment is necessary for appropriate management and evaluation of prognosis in any newborn infant with findings suggestive of either condition.

Beals and Hecht described the syndrome 'congenital contractural arachnodactyly' (CCA) as a dominantly inherited disorder of connective tissue characterised by multiple contractures, arachnodactyly, dolichostenomelia, scoliosis, and external ear anomalies.¹ With increasing numbers of cases reported, the occasional association of cardiac anomalies with CCA has been repeatedly documented.²⁻⁷ Additional case reports have also emphasised the difficulty of distinguishing CCA from infantile Marfan's syndrome,⁸⁻¹¹ which also carries a low but significantly increased frequency of cardiac anomalies other than those associated with progressive valvular and aortic disease.^{12, 13} We report a well documented case of CCA in whom multiple congenital cardiac malformations were recognised in the newborn period, but progressive vascular changes more characteristic of infantile Marfan's syndrome eventually compromised airway patency and contributed to the child's early death. Literature review and our experience indicate that there is a subset of infants with major cardiac malformations whose presentation may be compatible with either infantile Marfan's syndrome or CCA, but is typical of neither. Our case underscores the need for early cardiac evaluation and regular echocardiographic monitoring in any infant presenting with features suggestive of either condition, as the presence of symptomatic heart disease in the first year of life is associated with a less favourable prognosis.

Case report

This infant boy was born at 37 weeks' gestation by elective caesarean section for breech presentation to a 25 year old woman who had had a previous caesarean section. There was no family history of significant congenital abnormalities and neither parent was noted to have marfanoid habitus or other features of Marfan's syndrome. Birth weight was 2300 g and Apgar scores were 7 and 9 at 1 and 5 minutes respectively. He was noted to be dysmorphic with retrognathia, crumpled ears, dolichostenomelia, arachnodactyly with flexion contractures of fingers, wrists, elbows, hips and knees, and kyphosis of the thoracic spine (fig 1).

His initial attempts to feed were unsuccessful, with frequent vomiting, and he was found on investigation to have duodenal atresia with malrotation. He also developed a hyperdynamic precordium with a systolic murmur, and an echocardiogram demonstrated an ostium primum atrial septal defect, a large inlet ventricular septal defect with discrete atrioventricular valves, a patent ductus arteriosus, hypoplasia of the aortic arch, and preductal coarctation. The aortic root dimension measured 1.0 cm (normal (2 SD)=1.01 cm (0.15)).¹⁴

Duodenoduodenostomy was performed on day 6 of life but postoperatively he developed intractable heart failure necessitating ligation of the patent ductus arteriosus, subclavian flap repair of the coarctation of the aorta, and pulmonary artery banding. His recovery was slow and he was eventually discharged at 3.5 months of age. Initial and subsequent ophthalmological examinations were normal with no evidence of lens dislocation, and cytogenetic analysis of chromosomes confirmed normal male karyotype (46, XY).

He next presented at 5 months of age with grey spells associated with stridor, cyanosis, bradycardia and apnoea, and subsequently required intubation and support with assisted ventilation. He had an active precordium and loud pulmonary flow murmur. Even though paralysed and ventilated, the grey spells continued, with bradycardia (<60/min) and falling oxygen saturation (<80%). The chest radiograph demonstrated left lingular and right lower lobe collapse, and an echocardiogram showed an appreciably dilated aortic root with the aortic root dimension now 1.7 cm (normal (2 SD)=1.21 cm (0.14))¹⁴ and similar appreciably dilated pulmonary arteries, both proximal and distal to the pulmonary artery band (fig 2). Flexible fiberoptic bronchoscopy demonstrated partial collapse of the distal half of the trachea to the

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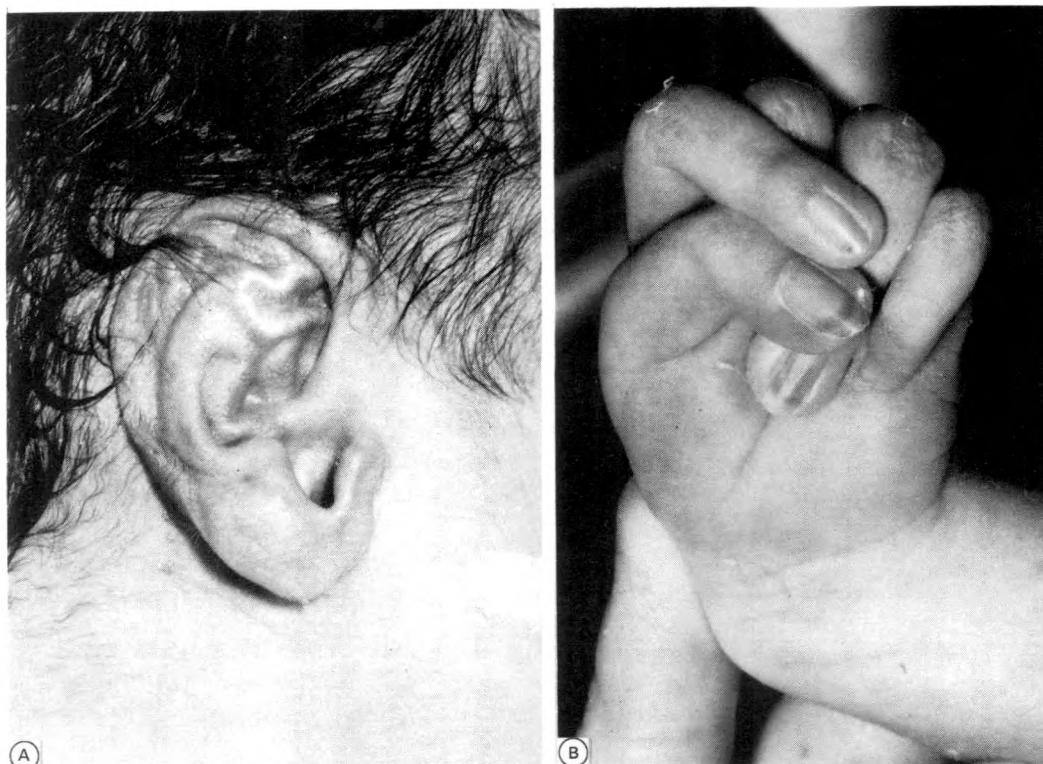


Figure 1 (A) Characteristic 'crumpled' ear deformity. (B) Arachnodactyly with flexion contractures of fingers and wrist.

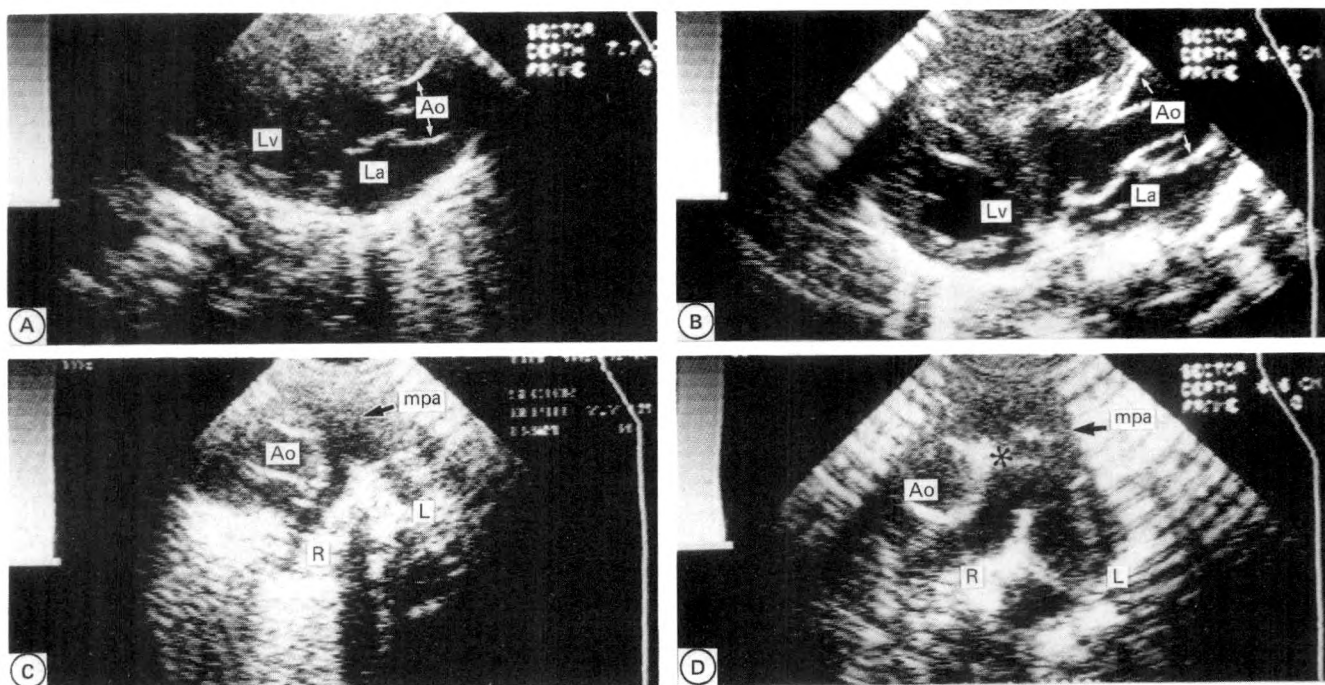


Figure 2 Echocardiogram. Parasternal long axis view at initial presentation (A), and at 5 months (B) illustrating appreciable dilatation of aortic root; white arrows define the inner margins of the aorta at the sinus of Valsalva. Parasternal short axis view at initial presentation (C), and at 5 months (D) illustrating appreciable dilatation of pulmonary arteries, proximal and distal to pulmonary artery band (*), compared with reference values.¹⁴ Ao, aorta; La, left atrium; Lv, left ventricle; L, left pulmonary artery; R, right pulmonary artery; mpa, main pulmonary artery.

carina, either due to or compounded by extrinsic compression from the grossly dilated great arteries. He gradually responded to medical treatment and support and was discharged from hospital at 6 months of age.

Over the next five months, he thrived poorly but no hospital admissions were required. He was normotensive and his family doctor noted no visual abnormalities. At 11.5 months of age he developed bronchopneumonia with increasing respiratory distress. He was treated with

antibiotics and supportive care but two days later had a further episode of airway obstruction with stridor and bradycardia from which he could not be resuscitated with intubation. No postmortem examination was performed.

Discussion

After the original description of the syndrome of CCA by Beals and Hecht in 1971,¹ Lipson *et al* described a case of CCA with Klinefelter's

syndrome and associated severe cardiovascular abnormalities.² The cardiac anomalies were atrial septal defect, ventricular septal defect, patent ductus arteriosus, and interruption of the aortic arch, a combination of lesions which is strikingly similar to the initial cardiac malformations found in our case (see table). Lipson *et al* first emphasised the importance of distinguishing the pattern of cardiac involvement in CCA from infantile Marfan's syndrome; Macleod *et al* reiterated this concern because of the less favourable prognosis in the latter.¹⁵ In a review of the literature Ramos Arroyo *et al* (table) found nine of 61 cases of CCA (15%) had cardiac malformations.³ Although six of the nine had mitral valve prolapse, no patients had dilatation of the aortic ring or aneurysm. Gruber *et al* reported a premature infant with CCA and severe heart failure due to mitral regurgitation, in whom appreciable dilatation of the aortic and pulmonary roots was detected at cardiac catheterisation.⁴ Subsequently, Bell and Wheller *et al* described an infant with CCA and severe dilatation of the roots of both great arteries with aortic insufficiency,⁵ and Huggon *et al* described an infant girl with CCA, iridodonesis, and mitral and tricuspid incompetence.⁶ All three infants died from cardiorespiratory failure. The occurrence of these severe cardiac lesions presenting in infancy, and the association of mitral valve prolapse with CCA,⁷ may make the distinction between CCA and infantile Marfan's syndrome more difficult to draw.

In a recent review, Geva *et al* summarised the cardiac abnormalities in 95 cases of infantile Marfan's syndrome¹³ (also tabulated in table). The most frequent lesion encountered was mitral valve prolapse (96%) but it was not clinically significant. However, mitral and tricuspid incompetence were prominent (84% and 31% of cases, respectively), and nearly all the fatalities were related to severe congestive failure secondary to atrioventricular valve

regurgitation. Although aortic root dilatation was also frequently observed (94%) and tended to progress, aortic valve regurgitation (25%) was less common than in adult patients with Marfan's syndrome. Pulmonary artery dilatation (25%) was also relatively frequent, in contrast to its rarity in adult patients.

Where cardiac disease is diagnosed early in life, cases tend to be more severe and there is a severely limited life expectancy, with most children dying in infancy.¹⁶ Echocardiography has increased the detection rate of mitral valve prolapse and progressive aortic root dilatation and there is convincing evidence that the mortality is roughly proportional to the degree of dilatation.^{17 18}

Our report documents the case of an infant with CCA where the cardiac manifestations comprised a combination of the pathological lesions characteristic of both Marfan's syndrome and CCA. The initial presentation was with structural anomalies more commonly described for CCA, consisting of atrial septal defect, ventricular septal defect, persistent ductus arteriosus, and coarctation of the aorta. However, the patient subsequently developed marked dilatation of the great arteries similar to the cardiac manifestations of Marfan's syndrome, and tracheal compression by the dilated great vessels contributed to airway compromise.

Previous reports indicating the importance of distinguishing CCA and infantile Marfan's syndrome, because of a better prognosis in the former, should be interpreted cautiously. Serious cardiac malformations can occur in CCA, and when significant symptoms appear in the first year of life, may prove rapidly fatal. Contrary to other reports, we found that congenital heart malformations do occur in patients with CCA. Moreover, a similar spectrum of malformations is a recognised, albeit lower frequency, finding in infantile Marfan's syndrome. There are case reports which raise the

Features of infantile Marfan's syndrome, CCA, and variants

	Infantile Marfan's syndrome ^{*12 13}	Congenital contractural arachnodactyly ^{*2 3 7 9}	Gruber <i>et al</i> ⁴	Bell and Wheller ⁵	Huggon <i>et al</i> ⁶	Present case
Diagnosis at birth	6/40 (15)	(100)	+	+	+	+
Family history	18/68 (26)	?	(-)	(-)	-	-
Contractures	6/9 (67)	64/64 (100)	+	+	+	+
Arachnodactyly	89/89 (100)‡	55/64 (86)	+	+	+	+
Ocular findings	59/73 (81)	(0)§	(-)	(-)	+	-
Cardiovascular (all)	(100)	9/61 (15)	+	+	+	+
Aorta						
Dilatation	76/81 (94)	0	+	+	(-)	+
Regurgitation	15/60 (25)	0	(-)	+	(-)	+
Mitral valve						
Prolapse	73/76 (96)	6	+	+	+	(-)
Regurgitation	64/76 (84)	0	+	+	+	(-)
Tricuspid valve						
Prolapse	27/51 (53)	0	+	+	-	(-)
Regurgitation	18/58 (31)	0	-	+	+	+
Pulmonary artery (dilatation or regurgitation)	14/57 (25)	0	+	-	(-)	+
Major anomalies			(-)	(-)	(-)	
Atrial septal defect	3/45 (7)	1	(-)	(-)	(-)	+
Ventricular septal defect	(-)	2	(-)	(-)	(-)	+
Patent ductus arteriosus	(-)	1	(-)	(-)	(-)	(-)
Other	2/9 (22)¶	1	(-)	(-)	(-)	+
Aortic arch interruption	(-)	1	(-)	(-)	(-)	
Non-cardiac anomalies	?	Klinefelter's syndrome, TOF with duodenal atresia	(-)	(-)	(-)	Duodenal atresia

*Results are No/total No (%); present, +; absent, -; absence inferred but not explicitly stated, (-).

‡Incidence based on assumption that arachnodactyly is part of the characteristic of musculoskeletal abnormalities.

§The report of apparent coincidence of CCA and Marfan's syndrome with ocular findings is not included.¹⁰

¶Includes two infants discovered with patent foramen ovale, and one infant with double orifice mitral valve, observed at postmortem examination.¹³

TOF, tracheo-oesophageal fistula.

question of what features decisively distinguish one condition from the other.

We would recommend careful echocardiographic examination and follow up of any child with congenital contractures and arachnodactyly in anticipation of significant cardiovascular complications appearing and progressing in a proportion of these children.

Neither our case nor the studies that precede it offer an obvious means of determining the extent of heterogeneity in the aetiology of either infantile Marfan's syndrome, congenital contractual arachnodactyly, or their intermediate variants. However, the localisation of Marfan's syndrome to chromosome 15 in families with adult Marfan's syndrome,¹⁹ and the mounting evidence for a central role of abnormal fibrillin protein in the pathogenesis of the connective tissue disorder,²⁰ should prove extremely useful in clarifying the apparent distinctions between these related disorders.

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Amniotic fluid *N*-acetyl- β -D-glucosaminidase activity and renal abnormalities

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Abstract

Amniotic fluid *N*-acetyl- β -D-glucosaminidase (NAG) activity was measured in 21 normal pregnancies to determine reference values, and in 10 pregnancies with fetuses who had prenatally recognised renal and urinary tract malformations. The normal values obtained at 17-19 and 28-31 gestational weeks did not differ, and an activity of 105 units NAG/mmol creatinine was the upper limit of the normal range. Raised NAG activities were found in four fetuses with oligohydramnios and severe bilateral renal disease, and also in two infants with a normal amount of amniotic fluid, only unilateral renal lesions, and a normal renal function after birth. Three of four cases with normal NAG activities had malformations without kidney damage, but one baby with prune belly syndrome was subsequently found to have dysplastic kidneys and renal failure. Our preliminary results suggest that a high level of NAG activity in the amniotic fluid indicates unilateral or bilateral kidney damage but is not proof of intrauterine renal failure.

The exact evaluation of fetal renal function and the demonstration of intrauterine kidney damage are two unsolved problems in the management of children with prenatal diagnosis of renal or urinary tract malformations. The extent of renal functional impairment seems to be best defined by the presence of oligohydramnios, as amniotic fluid is predominantly a result of fetal urine production.¹ Determination of sodium and osmolality of the fetal urine are widely accepted as the most reliable additional parameters.^{2,3} Analysis of fetal urine necessitates the puncture of the fetal bladder or the renal pelvis. Amniocentesis is less difficult and dangerous but no reliable indicator of fetal renal disease has so far been found in the amniotic fluid. In the present study we measured *N*-acetyl- β -D-glucosaminidase (NAG) activity in amniotic fluid in a control group undergoing amniocentesis, mostly for genetic counselling,

to determine the reference values. These results were compared with NAG activities in 10 cases with prenatally recognised urinary tract malformations to determine the value of NAG activity for the evaluation of fetal renal function and for the detection of intrauterine kidney damage.

Patients and methods

Amniocentesis was performed as a routine procedure in 21 pregnancies for genetic counselling or monitoring of suspected rhesus incompatibility. These patients served as the control group, and 15 of them had sampling between 17 and 19 weeks of gestation, and six between 28 and 31 weeks of gestation (table 1). Renal malformations were excluded in all fetuses by sonography.

The activity of NAG in the amniotic fluid was measured photometrically (Boehringer, Mannheim, Germany) with cresol-sulfonphthalein-glucosaminide as substrate, as previously described.⁴ Creatinine was measured by auto-analyser using the kinetic Jaffé reaction. The NAG values were expressed as units per litre (U/l) and standardised for creatinine (U/mmol creatinine). Values exceeding two standard deviations above the mean were defined as increased.

Analysis of amniotic fluid was also performed in 10 pregnancies with prenatally recognised or suspected renal malformations. The data for these cases are summarised in table 2. Elective abortion was performed in three pregnancies and two infants died shortly after birth. Necropsy or postnatal investigations confirmed the renal malformations in all except case 10, where normal kidneys were found.

Cases 1-4 suffered from the most severe malformations and oligohydramnios was noted in all. Case 5 had prune belly syndrome with immature but normally developed kidneys on histological examination. Cases 6 and 7 are examples of malformations with unilateral loss of renal parenchyma. In contrast, ureteropelvic junction obstruction present in case 8 caused no renal

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Table 1 NAG in amniotic fluid. Results of the control group shown as mean (SD) and range

Gestational age (weeks)	No of cases	NAG		Creatinine (μ mol/l)
		U/mmol creatinine	U/l	
17-19	15	73.81 (12.39) 45.20-91.10	4.59 (0.81) 2.80-5.95	62.33 (5.96) 53-70
28-31	6	59.97 (21.43) 31.90-81.90	5.38 (1.71) 2.55-7.00	91.50 (14.21) 80-115
Total	21	69.86 (16.23) 31.90-91.10	4.81 (1.15) 2.55-7.00	70.66 (16.05) 53-115

Table 2 Clinical data and NAG activity of 10 cases with prenatally suspected renal disease

Case No	Gestational age (weeks)	NAG		Prenatal findings	Outcome	Definitive diagnosis
		U/mmol creatinine	U/l			
1*	24	337·10†	23·20†	Polycystic kidneys	Abortion	Infantile polycystic kidney disease
2*	18	181·70†	10·90†	Bilateral hydronephrosis	Abortion	Posterior urethral valve, dysplastic kidneys
3*	32	151·40†	10·60†	Small, echodense kidneys	Died at 2 days of age	Dysplastic kidneys, pulmonary hypoplasia
4*	37	305·60†	27·50†	Multicystic right kidney	Died at 26 days of age	Multicystic right and dysplastic left kidney, trisomy 21
5	15	80·00	4·00	Enlarged bladder	Abortion	Prune belly syndrome, normal kidneys
6	31	116·25†	9·30†	Bilateral hydronephrosis and hydroureter	Alive	Bilateral vesicoureteric reflux grade 5, dysplastic left kidney
7	30	205·00†	12·30†	Left hydronephrosis	Alive	Multicystic-dysplastic left kidney
8	27	46·00	4·60	Left hydronephrosis	Alive	Obstruction of left ureteropelvic junction, normal kidneys
9	20	79·30	5·55	Fetal ascites, enlarged bladder	Alive, renal failure	Prune belly syndrome, dysplastic kidneys
10	33	65·00	5·20	Large, echodense kidneys	Alive	Normal kidneys

*Oligohydramnios.

†Increased NAG values.

lesion. Case 9 had prune belly syndrome, with fetal ascites, a patent urachus, and normally developed kidneys without hydronephrosis at the time of investigation. Eight weeks later, oligohydramnios and bilateral hydronephrosis were noted, but no fetal ascites. Investigations after premature delivery at 32 gestational weeks showed dysplastic kidneys which led to renal failure, and severe urethral stenosis.

Fully informed consent of the parents was obtained for all investigations. Student's *t* test was used for statistical analysis.

Results

The results of the control group are listed in table 1. NAG values were not statistically different in the two age groups although the values obtained between 28 and 31 gestational weeks were slightly higher if expressed as units per litre. In contrast, creatinine values were significantly higher in the later gestational weeks ($p < 0.01$). According to these findings, NAG values of 105 U/mmol creatinine were defined as the upper limit of the normal range.

NAG activity was raised in all four cases with oligohydramnios (cases 1–4) and severe bilateral renal disease. Two infants with unilateral renal lesions on postnatal investigation (cases 6, 7) also had raised NAG values, while three with normal kidneys had normal NAG activities despite malformations in two of them (cases 5, 8). Yet there was one infant (case 9) with prune belly syndrome who had a normal NAG activity but was found after birth to have badly damaged dysplastic kidneys and renal failure.

Discussion

NAG is a lysosomal enzyme which is present in high concentrations in renal tubular cells. Normally only small amounts are excreted into the urine. The excretion rate is not affected by serum concentrations as NAG is not filtered by the glomeruli. Raised urinary NAG values are found in various renal diseases. They reflect the activity of the disease and indicate renal damage.^{5, 6} Amniotic fluid is mostly composed of fetal urine and therefore NAG is found as a

normal constituent. Recently Agosti *et al* found constant NAG activities in the amniotic fluid between 16 and 19 weeks of gestation.⁷ Our data confirm these findings and in addition suggest similar NAG values in later stages of pregnancy. The slightly higher values of NAG if expressed as U/l and of creatinine obtained between 28 and 31 weeks of gestation could reflect the fetal growth and the greater mass of the fetal kidneys, but this difference is excluded if NAG is standardised for creatinine.

NAG isoenzyme studies showed that amniotic fluid as well as the urine of neonates exclusively contain the B-isoenzyme.⁷ This finding indicates that fetal urine production is actually the main source of NAG in amniotic fluid. Amniotic cells express lysosomal enzymes, including NAG activity. No conclusive information is yet available on how much NAG activity may originate from these cells, especially in a pathological state.

Despite these considerations, our results seem to indicate that an increased NAG activity in the amniotic fluid is associated with intrauterine renal disease. Increased NAG activities were found not only in the most severe cases with bilateral renal disease and oligohydramnios (cases 1–4) but also in two cases with a normal amount of amniotic fluid, only unilateral loss of renal parenchyma, and a normal renal function after birth being provided by the contralateral kidney (cases 6, 7). One of these had a non-functioning unilateral multicystic kidney. Increased NAG activity could be interpreted as a severe ureteropelvic junction obstruction causing the complete destruction of the kidney. These two cases are particularly important. They show that an increased NAG activity is no proof of intrauterine renal failure. Rather it seems to indicate that kidney damage is present or developing. Therefore this test could be helpful in distinguishing fetuses with malformations leading to intrauterine loss of renal parenchyma from fetuses with malformations which are, at least at the time of investigation, not harmful for the kidneys and the renal function. Case 9 had a normal NAG activity despite severe renal disease after birth. Our speculation is, that at the time of amniocentesis

the patent urachus served as a urinary drainage enabling a normal renal development, and that the loss of renal parenchyma took place after its closure.

Our study was performed in a small number of cases and the results are preliminary. However, further investigations seem to be justified as this test could be helpful in clarifying some aspects of intrauterine renal disease.

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Factors influencing plasma renin and renin substrate in premature infants

Terence J Stephenson, Fiona Broughton Pipkin, Alun C Elias-Jones

Abstract

Concentrations of plasma renin (PRC) and plasma renin substrate (PRS) were measured during the first week of life in 52 infants born at less than 37 weeks' gestation (mean (SEM) gestation 30 (0.4) weeks, mean (SEM) birth weight 1.35 (0.08) kg). Both PRC (median 35, interquartiles 16.3, 94.5 ng/ml/hour) and PRS (median 2.3, interquartiles 1.3, 5.0 µg/ml) were raised compared with adults. The proportional rise in PRC was much greater than that in PRS, suggesting that PRS may be rate limiting in the generation of angiotensin I. Log₁₀ PRC was inversely proportional to gestational age and a high urinary sodium loss was associated with a significantly raised log₁₀ PRC. In hypoxaemic infants, there was a strong correlation between log₁₀ PRS and haemoglobin concentration; this is a new observation in human infants but consistent with data available from other species.

The renin-angiotensin system in adult man is concerned with the maintenance of intravascular fluid volume, blood pressure, and sodium and potassium homeostasis. However, studies in a number of different species have suggested that the renin-angiotensin system may have a more important role early in phylogeny and ontogeny,^{1 2} periods during which the more sophisticated autonomic nervous system is less well developed.

A number of investigators have studied the renin-angiotensin system in the newborn human infant since it was first observed that umbilical venous renin concentration exceeded maternal venous renin concentration.³ However, these studies have reported plasma renin activity (PRA), rather than plasma renin concentration (PRC) and plasma renin substrate (PRS) independently.⁴⁻⁷

PRA is a measure of the rate of generation of angiotensin I by a plasma sample under specified conditions; PRA may thus be low because of either relatively low enzyme or relatively low substrate concentrations. The reaction between the enzyme renin and its substrate appears to follow first order kinetics in adult man, with the enzyme being rate limiting.⁸ However, in human pregnancy, even though PRS is raised, it is the substrate which is rate limiting in the mother.⁹

Very little is known in the human neonate about the relative contributions of PRC and PRS to the raised PRA observed in newborn infants^{5 7} and whether PRC or PRS is rate limiting. PRC and PRS are under different control mechanisms.^{10 11}

The purpose of this study was to measure simultaneously PRC and PRS in premature newborn infants during early postnatal life and to examine the relationship of PRC and PRS to blood pressure and concentrations of urea, electrolytes, and arterial blood gases. These variables are known to relate to the renin-angiotensin system from previous studies of PRA in animals,^{12 13} adult man,^{14 15} and the human fetus^{2 3 9} and newborn.^{4-7 10 11 16}

Subjects and methods

SUBJECTS AND SAMPLES

The protocol was approved by the Nottingham hospitals' committee of ethics.

All babies born at less than 37 weeks' gestation were deemed to be eligible for the study if arterial cannulation was required during the first week of life. This selection criterion was necessary because it was not considered ethical to obtain samples by direct venepuncture. Gestation was derived from the date of last menstrual period if known. Otherwise, gestation was assessed by ultrasound morphometry in early pregnancy or, failing this, postnatal Dubowitz scoring.¹⁷

Blood samples (maximum 2.5 ml) were collected from an infant at 9 am on the first morning on which an arterial catheter was in place. If the infant was male, a six hour urine collection was made by attaching a polythene bag over the genitalia, starting the collection from the time at which blood was taken.

If the arterial catheter remained in place 48 hours later, and if the infant was still within the first week of postnatal life, further blood and urine samples were obtained.

ANALYSIS OF SAMPLES

An aliquot of 0.125 ml of blood was taken into a heparinised, sealed syringe and arterial blood gases measured immediately (Corning 168 pH/Blood Gas system, Corning Medical and Scientific). Another aliquot of 1.0 ml of blood was taken into a tube containing lithium heparin for subsequent measurement of plasma sodium, potassium, urea and creatinine concentrations (Corning 902 analyser, Corning Medical and Scientific). Plasma osmolality was measured by the depression of freezing point method (Freezing point osmometers, Advanced Instruments Ltd). A further aliquot 0.3 ml of blood was taken into a tube containing potassium EDTA for subsequent measurement of haemoglobin concentration (Coulter S+4 cell counter, Coulter Electronics Ltd). A final aliquot of

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1.0 ml of blood was taken into potassium EDTA, the sample centrifuged, and the plasma separated immediately. The plasma was frozen for later measurement of PRC and PRS, at physiological temperature and pH, by established radioimmunoassay methods already published.¹⁸ The high PRC found in many samples necessitated the use of shorter incubation times than usual (0, 15, 30, and 45 minutes). The intra-assay coefficient of variation for PRC and PRS were 4.4 and 5.1% respectively; interassay coefficients of variation were 14.5 and 13.5%.

The volumes of the six hour urine collections were recorded and the samples assayed the same day for sodium, potassium, urea, and creatinine concentrations (Corning 902 analyser, Corning Medical and Scientific). Osmolality was measured by depression of freezing point.

Systolic and diastolic blood pressure were measured immediately before blood sampling using either the oscillometric technique (44 babies; Dynamap Neonatal Vital Signs Monitor, Critikon Inc) or the direct intra-arterial measurement (eight babies; pressure transducer at heart level coupled to S and W monitor, S and W Medico Teknik A/S).

ANALYSIS OF DATA

Creatinine clearance and fractional excretions of sodium and potassium were calculated from the data obtained in this study. A correction was applied to the small number of blood pressures measured intra-arterially to allow comparison with the larger number of measurements made oscillometrically.¹⁹

Analyses were performed using the SPSSX statistical package. Where appropriate, data were transformed logarithmically before analysis to achieve a more normal distribution. This is a standard statistical tool which is frequently necessary with skewed biological data. If this failed to normalise the data, non-parametric analyses were used. Arithmetic or geometric means were calculated. Arithmetic means (SEM) are quoted. Medians and interquartiles are quoted for non-normally distributed data. Comparisons were made using paired or unpaired *t* tests as appropriate and correlation coefficients calculated by method of Pearson. The straight line equations shown in figs 1–3 were generated by linear regression analysis.

Results

Blood samples were obtained from 52 infants, 28 boys and 24 girls, mean (SEM) gestation 30.0 (0.4) weeks, mean (SEM) birth weight 1.35 (0.08) kg. Ten infants had birth weights below the third centile for gestation age,²⁰ of whom only one was born at less than 28 weeks' gestation. The mean (SEM) postnatal age was 2.4 (0.2) days. A second blood sample was obtained 48 hours later from 31 babies; these paired data are considered separately below. Urine collections were made from 25 boys but data were incomplete for four of these. A further urine sample was obtained 48 hours later from 12 of these infants (see methods). As

would be expected, both systolic and diastolic blood pressures rose significantly ($p < 0.0001$, $p < 0.02$) with increasing gestational age at delivery. The serum osmolality fell appreciably with increasing gestational age ($p < 0.0001$).

ENZYME

The median PRC at the time of first sampling was 35.0 (16.3, 94.5) ng/ml/hour, significantly higher than in a group of 26 healthy young adults (2.4 (1.7, 3.3) ng/ml/hour; $p < 0.0001$). (We have no data on PRC and PRS concentrations, using the current assays, in normal term infants.) $\log_{10}$ PRC fell significantly with increasing gestation age ($p < 0.02$; fig 1). However, there was no independent association between $\log_{10}$ PRC and body weight ($p = 0.682$). There was also a significant positive correlation between $\log_{10}$ PRC and $\log_{10}$ fractional sodium excretion ($\log_{10}$ FeNa; fig 2, $p < 0.05$). There were no apparent associations between $\log_{10}$ PRC and either systolic or diastolic blood pressure, pH, blood gas tensions, or glomerular filtration rate.

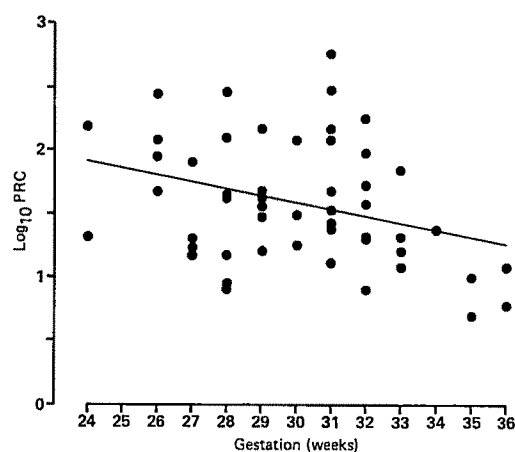


Figure 1 Association between $\log_{10}$ PRC and gestation showing significant inverse correlation over the range studied in this paper ($r = 0.33$; $p < 0.02$). $\log_{10}$ PRC (ng/ml/hour) = $3.25 - 0.06$ gestational age (weeks).

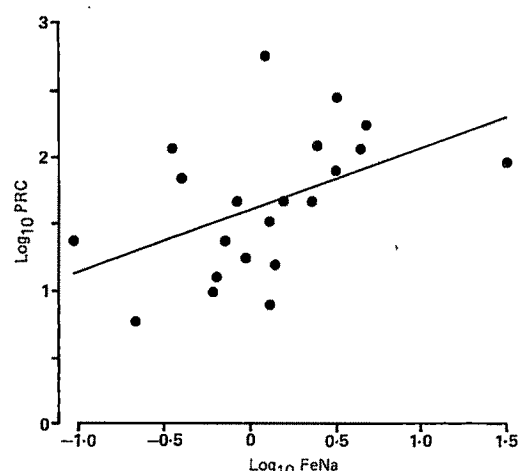


Figure 2 Association between $\log_{10}$ PRC and $\log_{10}$ fractional excretion of sodium (FeNa) determined in 21 of the boys at a mean (SEM) postnatal age of 2.4 (0.2) days. The $\log_{10}$ FeNa was positively correlated with $\log_{10}$ PRC ($r = 0.47$; $p < 0.05$). $\log_{10}$ PRC (ng/ml/hour) = $1.63 + 0.47 \log_{10}$ FeNa (%).

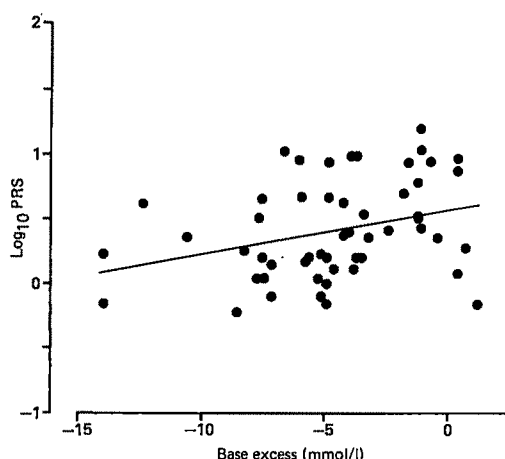


Figure 3 Association between $\log_{10}$ PRS and base excess showing a significant correlation between these two variables, ($r=0.32$; $p<0.02$). $\log_{10}$ PRS ($\mu\text{g/ml}$) = $0.59 + 0.04$ base excess (mmol/l).

SUBSTRATE

The median PRS at the time of first sampling was 2.3 ($1.3, 5.0$) $\mu\text{g/ml}$, significantly higher than that in healthy young adults (1.1 ($0.8, 1.2$) $\mu\text{g/ml}$; $p<0.001$). $\log_{10}$ PRS did not alter significantly with gestational age, indices of renal function, or blood pressure. However, a significant positive correlation was observed between $\log_{10}$ PRS and base excess ($p<0.02$; fig 3), although there was no correlation with pH or blood gas tensions. Nineteen of the premature infants who were severely hypoxaemic at the time of study (arterial oxygen tension (PaO_2) <7.2 kPa) were found to show a significant positive correlation between $\log_{10}$ PRS and haemoglobin ($p=0.001$) and packed cell volume ($p=0.003$). This association was not seen in 16 premature but normoxaemic infants of similar gestation ($\text{PaO}_2 >9.0$ kPa).

PAIRED DATA

Paired data on PRC and PRS were available from 31 infants. Median PRC fell between the first sample and the second sample by 6.0 ($-36.0, +12.0$) ng/ml/hour but this fall was not significant. Median PRS also fell slightly, by 0.3 ($-0.8, +1.5$) $\mu\text{g/ml}$, but this change was also not significant. There were no significant changes over the period studied in arterial blood pressure, blood gas tensions, or packed cell volume.

Discussion

LIMITATIONS OF THE STUDY

Because of the ethical constraints of investigating only those infants with an indwelling arterial catheter, the sample studied was not representative of the population of all infants born prematurely, although the more immature the infant, the more representative the sample becomes. All umbilical arterial catheters were sited with the tip above the level of the diaphragm but we cannot exclude the possibility that the presence of an umbilical arterial catheter may alter renal blood flow. Ideally, serial daily samples would have been obtained, but again this could not be justified ethically, and 24 hour

urine collections would have been obtained from all infants enrolled in the study. However, it was felt that the technique of bag urine collection was only reliable in boys. A six hour period was considered the most feasible duration for which the bag could be kept attached and the urine uncontaminated. As fluid compartments in the neonate correlate closely with body weight, all parameters are expressed per unit body weight.²¹

ENZYME AND SUBSTRATE

The measurement of PRA gives an idea of the angiotensin I generating capacity of a plasma sample. Assuming that angiotensin converting enzyme activity is not rate limiting, this thus gives information about the angiotensin II generating capacity, which is, of course, of direct biological interest in the absence of a direct measurement of angiotensin II. In the non-pregnant adult PRC appears to be rate limiting in the enzyme:substrate reaction and changes in PRA thus follow closely those of PRC. In pregnancy and the neonate, however, it appears to be PRS which is rate limiting⁹ so that interpretation of underlying changes in enzyme and/or substrate synthesis or release becomes impossible. Enzyme and substrate are regulated by different mechanisms, and it was thus of interest to determine the individual plasma concentrations of PRC and PRS, and to attempt to correlate them with potential stimuli for release.

In the human neonate, it has been shown that PRA is high at birth⁵ and higher the earlier the gestation.⁷ PRA falls with increasing postnatal age^{5,6} and this trend continues throughout infancy and childhood. In the newborn puppy²² and rat,²³ however, there is a further postnatal increase in PRC before the decline to adult values and this delayed increase in renin concentration may reflect the relative immaturity of these mammals at birth. PRA has been shown to be inversely correlated with sodium intake and directly correlated with urine osmolality over the first week of postnatal life in term infants.¹⁶ PRA also appears to increase in response to hypovolaemia, at least after 31 weeks' gestation.²⁴ These studies therefore show that, at least by the last trimester, the renin-angiotensin system can be activated by similar stimuli to the adult.

Our data have now shown that PRC can be extremely high in premature infants in the first few days of postnatal life, considerably higher than in term infants.²⁵ Symonds *et al* measured PRC in samples obtained at cordocentesis between weeks 16 and 24 and also found PRC to be high (approximately 26 ng/ml/hour).²⁶

It appears from our data that although PRS is somewhat higher in premature infants than at term²⁷ or in later life, PRS is nevertheless probably rate limiting in the generation of angiotensin I in vivo at this gestation, given the proportionately much higher concentrations of PRC. The large volumes of blood which would be needed for formal kinetic studies in the infant make such studies impossible at present. Investigation of the postnatal development of

the renin-angiotensin system in the rat also suggested that plasma renin substrate concentration may be rate limiting in the newborn rat but not in the adult.²³ Symonds *et al* reported PRS concentrations within the normal adult range in the samples obtained at cordocentesis.²⁶ It is not possible to determine from our data whether the higher PRS which we found at a later gestation (measured in the same assay system) is a consequence of increasing gestation or of premature delivery. PRS is an α_2 globulin synthesised by the liver and the rise in PRS concentration with gestation may simply reflect a maturation of hepatic globulin production. Alternatively, less substrate may be consumed as PRC falls during the last trimester.

CHANGES IN RELATION TO RENAL FUNCTION

The relationship demonstrated in this study between PRC and gestation shows an inversality common to all large mammalian species studied in late gestation,² and this may be related to maturing nephrogenesis, which is complete by 36 weeks' gestation in the human. Urinary aldosterone excretion increases significantly between 30 and 41 weeks' gestation,⁷ and the urine potassium to sodium ratio, an index of aldosterone dependent distal tubular activity, is positively correlated with conceptional age.²⁸ Therefore, as gestation proceeds, glomerulo-tubular balance improves, renal sodium re-absorption increases, and renin concentrations fall.

This concept of end organ insensitivity driving the renin-angiotensin system in the more premature infants is supported by the data in fig 2. When the fraction of filtered sodium appearing in the urine was high, PRC was also high. Previous work has shown that premature infants can increase PRA in response to a negative sodium balance,^{7 29} but the high renal sodium losses of immature infants are due in part to a blunting of aldosterone synthesis or release and in part of the limited responsiveness of the distal tubule to aldosterone stimulation.³⁰⁻³²

OTHER FACTORS WHICH MAY ACTIVATE THE RENIN-ANGIOTENSIN SYSTEM

The renin-angiotensin system is known to be activated via β adrenergic stimulation in the adult.^{32 33} It has also been observed that angiotensin II concentrations, which parallel PRA in infancy,³⁴ are significantly raised in infants with severe respiratory distress syndrome,³⁵ and the severity of respiratory distress syndrome increases with decreasing gestation. This study did not show any significant association between PRC and blood pressure or arterial blood gas tensions and in a previous study of 11 term infants with congestive cardiac failure and raised values of PRA, no relationship was found between PRA and systolic or diastolic blood pressure.³⁶

ENZYME, SUBSTRATE, AND HAEMOGLOBIN

We report for the first time a correlation between $\log_{10}$ PRS and both packed cell volume

and haemoglobin concentrations in hypoxaemic premature infants. We have recently made a similar observation in prematurely delivered pony foals (F Broughton Pipkin, J Ousey, and P Rossdale, work in progress). PRS and erythropoietin are both α_2 globulins, both are manufactured in the liver and show apparent close structural homology,³⁷ both are activated by a renal factor, and both are higher in the newborn than in later life. Circumstantial evidence for a relationship between oxygen delivery and the renin-angiotensin system comes from data from chronically hypoxic rats in which PRS concentrations were raised and correlated closely with erythropoietin concentrations.³⁸ Similarly, the renin-angiotensin system can be activated in adult man by chronic altitude exposure.³⁹

CLINICAL RELEVANCE

We have confirmed that the renin-angiotensin system is very active in premature human infants. What remains unclear is whether this is desirable. It is possible that an activated renin-angiotensin system is an appropriate response to the low blood pressure,³⁵ low glomerular filtration rate,⁴⁰ and glomerulotubular imbalance⁴¹ of early postnatal life. However, angiotensin II is the most potent circulating vasoconstrictor known, and acts as a pulmonary vasoconstrictor in adult man⁴² and in fetal lambs⁴³ and the high concentrations of angiotensin II associated with respiratory distress syndrome³⁵ may exacerbate pulmonary hypertension and salt and water retention.⁴⁴ The consequences of an activated renin-angiotensin system for the premature cerebral circulation are unclear. Leslie *et al* have recently reported high PRA in 10 very low birthweight infants who had suffered severe intraventricular haemorrhage during the first two days of postnatal life.⁴⁵ Eight of the infants we studied had also suffered moderate to severe intraventricular haemorrhage during the first week. Six of these had PRS above the group median and four had grossly raised PRC (>120 ng/ml/hour).

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Diamorphine infusion in the preterm neonate

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Abstract

The effects of diamorphine were studied in 34 premature neonates who were given a loading dose of 50 µg/kg of diamorphine followed by a constant rate intravenous infusion of 15 µg/kg/hour. Small but significant falls were noted in blood pressure (at 30 minutes) and heart rate (at 30 minutes, six hours, and 12 hours) after administration of diamorphine, but these did not appear to cause any clinical deterioration and were thought to be related to the sedative effect of the drug. A significant fall in respiration rate at 30 and 60 minutes reflected the desired intention to encourage synchronisation of the infants' breathing with the ventilator. The mean (SD) plasma concentration of morphine measured during the infusion at steady state was 62.5 (22.8) ng/ml (range 20 to 98 ng/ml). The data suggest that this dosage regimen of diamorphine is safe. It results in plasma concentrations of morphine in the premature neonate which are comparable with those that are known to provide effective analgesia in the child and adult.

Until recently it was believed that newborn infants did not feel pain and consequently the use of analgesics in neonatal units was limited. It is now accepted that pain pathways are well developed in newborn babies and that an acute stress response to pain is readily detected as hormonal and metabolic changes.¹ There is good evidence that the use of opioid analgesic infusions reduces this stress response in preterm infants undergoing surgery² and as a result there is increasing use of opioids as analgesia in neonatal units. In addition, opioids are now being used more frequently as a sedative in mechanically ventilated newborn infants. This practice is believed to improve the synchronisation between the infant's own breathing and the ventilator. As well as these potentially beneficial effects, opioids do have unwanted side effects^{3,4} and care must be taken to ensure that the chosen dosage regimen does not cause unnecessary danger to the patient.

Diamorphine (3,6-diacetylmorphine) is a synthetic derivative of the opioid morphine. In man, diamorphine is rapidly metabolised to 6-acetylmorphine and morphine⁵ and it is generally accepted that diamorphine acts as a pro-drug for its active metabolites.^{6,7} Diamorphine has been reported to be a faster acting and more potent analgesic than morphine, features thought to derive from its more rapid uptake into the brain due to its increased lipid solubility compared with morphine.⁸ In addition, the

increased aqueous solubility of diamorphine compared with morphine is advantageous for intravenous administration. Diamorphine infusion is currently in use clinically to treat both mature and premature newborns, the diamorphine dosing regimen being based on that for morphine. This study was designed to evaluate the effect of diamorphine and to establish the safety of our current dose regimen in the premature neonate.

Patients and methods

PATIENTS

Thirty four neonates of gestational age 26 to 40 weeks (mean (SD) of 31.0 (4.0) weeks), postnatal age 1 to 37 days (mean (SD) 3.0 (6.1) days) and birth weight 740 to 3560 g (mean (SD) 1610 (710) g) were studied. Thirty of the infants had respiratory distress syndrome, and the remaining four were diagnosed as suffering from apnoea, perforated caecum, tracheo-oesophageal fistula, and meconium aspiration. Approval for the study was obtained from the hospital ethics committee and informed consent was given by parents.

DOSE REGIMEN AND OBSERVATIONS

Patients received a loading dose of diamorphine of 50 µg/kg given as an intravenous infusion over 30 minutes, followed by a continuous infusion at a rate of 15 µg/kg/hour. The loading dose and the continuous infusion rate were based on the lowest recommended doses for morphine administration, to take into account the reported higher potency of diamorphine compared with morphine.⁹⁻¹² Diamorphine hydrochloride was diluted in 10% dextrose and infused at a rate of 0.5 ml/hour to keep the volume of fluid administered to a minimum. For clinical reasons certain patients received a different loading dose or infusion rate of diamorphine, and in some patients the infusion rate was changed during the study. The duration of the diamorphine infusion ranged from 14 to 149 hours (mean (SD) 59.4 (32.9) hours).

Observations were carried out on 34 infants, 20 of whom were studied closely in the first 24 hours after the loading dose of diamorphine, the remainder had normal regular nursing observations during the infusion and for 24 hours after the end of the infusion. In the closely studied group, measurements of mean blood pressure, heart rate, respiratory rate, temperature, arterial pH, oxygen tension (P_O₂), carbon dioxide tension (P_{CO}₂), and blood glucose concentration were made before the loading dose of diamor-

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phine and at 30 minutes, one, six, 12, and 24 hours after the dose.

BLOOD SAMPLING AND ANALYSIS

Arterial blood samples (0.5 ml) were collected after the loading dose, two to five times during the continuous infusion, and serially 10 times in the 24 hours after discontinuation of the diamorphine infusion. Plasma was separated and stored at -30°C until analysed. Plasma from eight subjects was analysed by a high-pressure liquid chromatography (HPLC) method for morphine and 6-acetylmorphine.¹³ This HPLC method involved solid phase extraction, fluorescent derivatisation, and fluorescence detection of morphine and 6-acetylmorphine in plasma. The limit of quantitation for the assay was 10 ng/ml for morphine and 25 ng/ml for 6-acetylmorphine (0.1 ml plasma volume). The remaining samples were analysed by a Coat-A-Count radioimmunoassay (RIA) method (Diagnostic Products Ltd) which was highly specific for morphine. The RIA method showed low cross reactivity ($<0.5\%$) with diamorphine, 6-acetylmorphine, and other metabolites of morphine. The steady state concentration was taken as the morphine plasma concentration at the end of the diamorphine infusion, or as a mean of values during infusion where these were within $\pm 10\%$ of each other. Good agreement was achieved between the RIA and HPLC methods. During the study, drugs other than diamorphine were administered to the infants, the most common being benzylpenicillin, gentamicin, flucloxacillin, metronidazole, and cefotaxime. There was no evidence that these drugs interfered with the assay for morphine in plasma.

Results

Table 1 shows the mean values compared with the predose values for heart rate, mean blood pressure, respiratory rate, blood pH, blood PO_2 , blood PCO_2 , and blood glucose. Blood pressure showed a transient reduction at 30 minutes ($p<0.03$) which was not maintained at one, six, 12, or 24 hours. There was a significant fall ($p<0.03$) in heart rate at 30 minutes and at six and 12 hours but significant differences were not observed at 60 minutes, 12, or 24 hours. A significant fall ($p<0.01$) in respiration rate was noted at both 30 and 60 minutes after infusion but this was not sustained later in the infusion. No significant differences were observed in arterial pH, PCO_2 , PO_2 , or in blood glucose for the duration of the study. Table 2 shows the

Table 2 Mean percentage changes in heart rate, mean blood pressure, and respiratory rate in 20 preterm infants after diamorphine loading and infusion. Each value is mean (SD)

Time from baseline measurement (hours)	% Change in heart rate	% Change in mean blood pressure	% Change in respiratory rate
0.5	-2.3 (4.5)*	-6.3 (11.6)*	-6.6 (9.5)**
1	-2.0 (6.1)	-4.5 (11.8)	-8.2 (12.0)**
6	-6.1 (9.5)**	-3.4 (16.3)	-1.7 (23.2)
12	-5.2 (8.3)*	-2.6 (17.2)	0.6 (30.4)
24	-4.2 (11.7)	4.3 (23.7)	5.0 (37.4)

Paired *t* test: * $p<0.05$, ** $p<0.01$.

mean percentage changes in heart rate, mean blood pressure, and respiratory rate: similar small but significant falls were noted.

Morphine was detected in the plasma of all subjects but no 6-acetylmorphine was detected in any of the plasma samples analysed by the HPLC method. The mean (SD) steady state morphine concentration during diamorphine infusion was 62.5 (20.8) ng/ml ($n=19$) with the plasma concentrations ranging between 20 and 98 ng/ml for those patients who received diamorphine at an infusion rate of 15 $\mu\text{g/kg/hour}$.

Discussion

Although small, significant falls in heart rate and mean blood pressure were noted during the diamorphine infusion, they were not associated with any clinical deterioration. They may have been related to the reduction of stress in the infants caused by the sedative and analgesic effects of the drug rather than being due to unwanted side effects. Although the mean blood pressure and heart rate of patients in the study are towards the limit of desirable values, they still fall within the normal range for premature infants.¹⁴ Similar but more appreciable reductions in heart rate and blood pressure have been noted by other workers studying opioid drugs, with particular concern if the dose was given as an intravenous bolus.^{3,4} The loading dose was given as a slow bolus over 30 minutes in our study, perhaps preventing any noticeable changes in these cardiovascular measurements.

The fall in respiration rate reflected the desired intention to settle the patients and encourage synchronisation of the infants' own efforts with the ventilator, which was achieved in 19 of the 20 babies studied by one hour after starting the diamorphine infusion. In this study direct measures of analgesic and sedative benefit were not made, although the subjects were noted to be more relaxed after the introduction

Table 1 Effects of diamorphine infusion in the preterm newborn. Each value is the mean (SD) of observations in 20 infants

Time of measurement (hours after start)	Heart rate (beats/minute)	Mean blood pressure (mmHg)	Respiratory rate (breaths/minute)	pH	PaO_2 (kPa)	PaCO_2 (kPa)	Blood glucose (mmol/l)
Predose	152.5 (14.1)	38.8 (7.4)	75.3 (16.1)	7.20 (0.10)	7.1 (2.4)	6.5 (1.8)	4.3 (1.6)
0.5	148.9* (15.3)	36.5* (8.5)	70.3* (17.4)	7.23 (0.11)	6.9 (2.3)	6.0 (1.9)	4.2 (1.7)
1	149.8 (16.8)	37.1 (8.4)	68.9* (17.3)	7.22 (0.11)	7.1 (2.2)	5.8 (1.8)	4.3 (2.0)
6	144.2* (16.6)	37.2 (5.5)	72.0 (19.3)	7.21 (0.11)	8.4 (3.4)	6.5 (1.7)	4.7 (2.0)
12	144.0* (12.7)	37.6 (6.4)	70.8 (17.8)	7.24 (0.10)	7.8 (1.3)	6.8 (1.9)	4.2 (1.6)
24	144.2 (13.0)	40.3 (7.9)	72.8 (19.1)	7.22 (0.11)	8.0 (1.8)	7.2 (2.6)	3.7 (1.7)

*Significant difference from predose value (two tailed Student's *t* test, $p<0.03$).

of the diamorphine infusions. Similarly, exact measurements of urine and stool outputs were not made, although urine retention and constipation are described with opiates.

The range of plasma morphine concentrations of between 20 and 98 ng/ml (mean 62.5 ng/ml) compares with reported minimum concentrations required for effective analgesia in children and adults of between 20 and 65 ng/ml.^{12 15 16} Thus it appears that the diamorphine infusion rate of 15 µg/kg/hour used in the study produces an effective plasma concentration of morphine, although this does not necessarily imply effective analgesia. It is not known whether the reported therapeutic plasma concentrations of analgesics in children and adults apply to newborn infants nor whether there is an increased sensitivity to the side effects of opioid drugs. In addition, there is no information on the extent to which the active metabolite of diamorphine, 6-acetylmorphine, enhances the analgesic effect of the main active metabolite, morphine. In this study no 6-acetylmorphine was detected in plasma after diamorphine administration but this was probably a result of the limited sensitivity of the assay. We are planning further investigations to clarify the relationship between plasma concentrations of the active diamorphine metabolites, morphine and 6-acetylmorphine, and the analgesic effect in the neonate. Morphine pharmacokinetics were examined in the present study and are reported elsewhere.¹⁷

Our study has shown that diamorphine can be safely given to preterm newborn infants as a combination of a slowly administered loading dose and a continuous infusion. It appeared to be effective, and resulted in plasma morphine concentration which in a child or adult would provide adequate analgesia.

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Imaging of neonatal arterial thrombosis

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Abstract

The case of a neonate who presented with symptoms of upper limb ischaemia related to spontaneous multiple arterial and venous thromboses that were demonstrated by colour Doppler sonography and digital subtracted angiography is reported. The presentation of limb ischaemia at birth may be the warning sign of simultaneous cerebral infarction.

Multiple thromboses of large arterial and venous vessels in the neonatal period, not related to umbilical catheterisation, are rare and there are variable clinical presentations. We describe an additional case in which the correct diagnosis was made in the perinatal period by colour Doppler sonography (CDS) and digital subtracted angiography (DSA).

Case report

A full term boy was referred to our institution at the age of 2 days because of the absence of spontaneous movement and cyanosis of the right arm. The pregnancy had been uneventful. A prolonged delivery was due to shoulder dystocia. Absence of spontaneous movement, cyanosis, and absence of a palpable pulse of the right arm suggested that the diagnosis was a

right brachial plexus injury but in view of cyanosis and the absence of both brachial and radial pulses echocardiography, CDS, and DSA of the aorta were carried out. A catheter was passed through the umbilical artery into the ascending aorta and DSA showed a failure of opacification of the brachiocephalic trunk with reversed flow through the right carotid and vertebral arteries (fig 1A and 1B). This was consistent with an obstructing thrombus in the brachiocephalic trunk. CDS demonstrated further thrombi at the emergence of the left common carotid artery (fig 2) and in the retrohepatic inferior vena cava. Contrast enhanced computed tomography (fig 3) showed a hypodense lesion in the area of the right middle cerebral artery with calcification, which was highly suggestive of a prenatal thromboembolic event. After intravenous anticoagulant treatment with heparin (10 U/kg hour) and aspirin (100 mg/kg/day) for 10 days, nicoumalone (0.2 mg/kg/day) was given for three months. Ten days after the first CDS, a second CDS showed the resolution of the left carotid artery thrombus and the persistence of a thrombosed brachiocephalic trunk. Normal movements of the right arm returned four days after the first CDS. Subsequently a left hemiparesis became apparent at 3 months of age; the child is now 23 months old and has a complete

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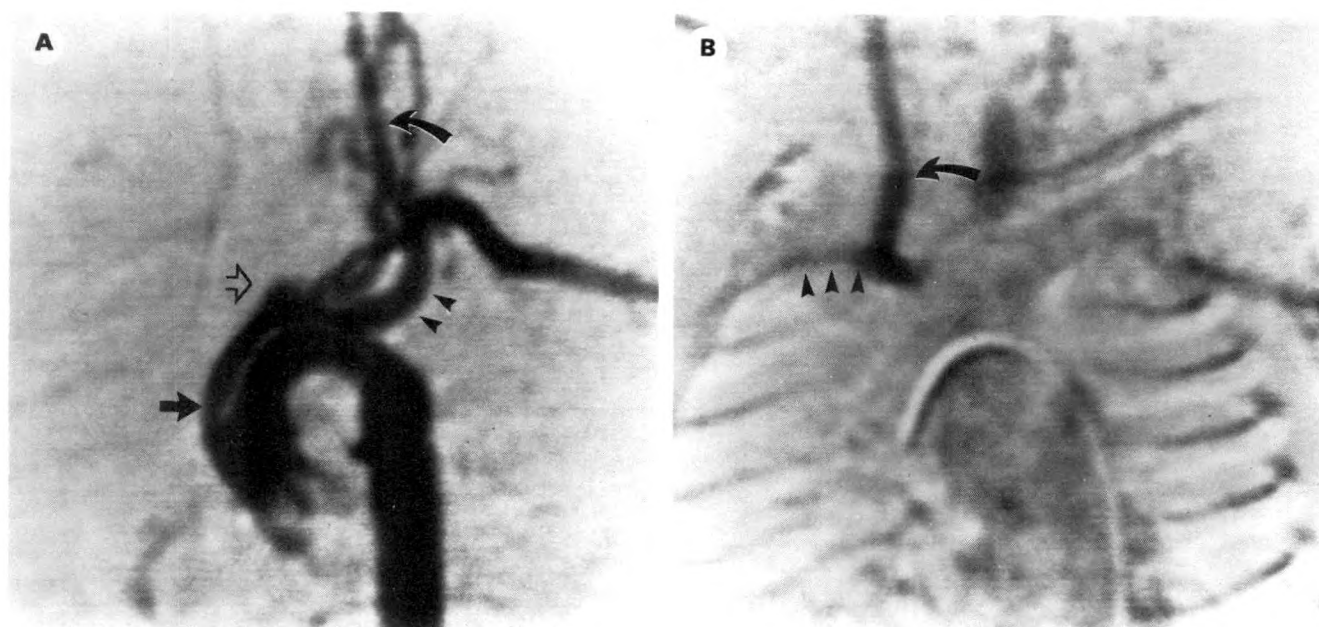


Figure 1 (A) Aortic DSA. The tip of the catheter has been placed in the ascendant aorta (large solid arrow). Opacification of the left subclavian (small arrows) and left carotid (curved arrow) arteries. Absent opacification of the brachiocephalic trunk (open arrow). (B) Late image showing opacification of the right subclavian artery (small arrows) via retrograde flow through the right carotid artery (curved arrow).

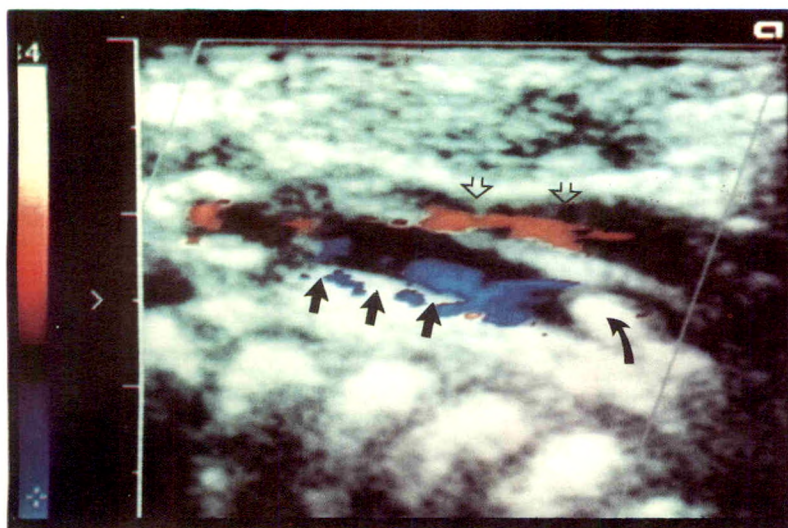


Figure 2 Sagittal CDS image of the left common carotid (solid straight arrows) with proximal partially obstructing mural thrombus (curved arrow). The arterial flow is blue and the venous jugular flow is red (open arrows).



Figure 3 Contrast enhanced cerebral computed tomogram demonstrating a superficial infarct in the territory of the middle carotid artery (open arrows). The atrophic aspect and the deep focal calcification suggest a prenatal ischaemic event. Cephalohaematoma (curved arrow).

left hemiplegia. There was no detectable coagulation abnormality, homocystinuria, or a deficit of protein C or antithrombin III in the infant or his family.

Discussion

Thrombosis of the aorta, great vessels, and veins in the neonatal period has been reported in association with the use of indwelling arterial

catheters.¹ Primary arterial and venous thromboses associated with antenatal stroke are rare and only two similar cases have been reported.²⁻³ Thrombosis of the ascending aorta has been encountered with early development of severe heart failure.³ Upper limb ischaemia at birth followed by hemiparesis has been reported.²

Aortic arch and great vessels thrombosis in the neonate is related to additional rare conditions like sepsis, dehydration, maternal diabetes, birth trauma, asphyxia, and aneurysmal ductus arteriosus. Some associations with homocystinuria, protein C and antithrombin III deficiency have been described¹⁻³ but were absent in the present case. Viral aortitis,³ thromboarthritis due to infantile periarteritis nodosa, and Kawasaki and Takayasu's disease must be considered in the differential diagnosis. In this case, the hypodense lesion in the area of the right middle cerebral artery was highly suggestive of a prenatal infarction, but was probably unrelated to birth trauma.

Many investigators consider ultrasound as the method of choice to visualise aortic arch obstruction and inferior vena cava thrombi.⁴⁻⁶ In the present case, CDS displayed the different arterial and venous thrombi and the reversed flow through the right carotid and subclavian arteries. Some authors recommend angiography as the definitive test for the diagnosis of arterial thrombosis.⁴⁻⁵ In the present case, DSA allowed us to confirm the findings of CDS without femoral puncture. The various attempted treatments have included surgical vascular repair, thrombolysis, prostaglandin E₁ infusion, or (as in our case) anticoagulant treatment. Renovascular hypertension, impaired renal function, and spastic hemiparesis are the most frequently described sequelae.²⁻⁴

In cases of perinatal upper limb ischaemia, CDS and DSA may provide important information about the site of obstruction. Obstructive lesions in relation to the great vessels derived from the aortic arch may be associated with cerebral infarction and so brain imaging should also be carried out.

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Intermittent fetal tachycardia and fetal hydrops

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Abstract

A case is reported where fetal hydrops was noted 10 days after an initial observation of intermittent fetal tachycardia at 31 weeks. A diagnosis of supraventricular tachycardia was made and a successful conversion to sinus rhythm was achieved with maternally administered flecainide, with subsequent resolution of the hydrops. The fetus required no further treatment in pregnancy or at follow up. The mother suffered no side effects of the treatment.

Fetal tachyarrhythmias are rare occurrences but can be fatal if not investigated and promptly treated. Although treatment has considerably improved fetal survival, the choice of antiarrhythmic agent is still controversial.

We describe a case of a fetus presenting initially with an intermittent tachyarrhythmia, the importance of which was not realised, which subsequently became a continuous supraventricular tachycardia resulting in fetal hydrops. The fetus was successfully treated with flecainide, a relatively new and effective treatment of tachyarrhythmias with associated fetal hydrops.

Case report

A healthy 29 year old woman, at 31 weeks in her second pregnancy, was noted to have an intermittent fetal tachycardia at a routine antenatal visit while on holiday. No further investigations, treatment, or referral was advised. Ten days later, when seen at her local hospital antenatal clinic, the fetal tachycardia was again noted, and an ultrasound scan revealed fetal hydrops. The patient was referred to the regional tertiary centre for further management. Ultrasound assessment revealed severe fetal hydrops with bilateral pleural, pericardial, and peritoneal effusions, and a tachycardia of approximately 300 beats/minute. The rate reverted to normal on one occasion during the initial assessment but this was short lived. M mode echocardiography confirmed a tachycardia of 300 beats/minute with a 1:1 relationship between atrial and ventricular conduction, consistent with a diagnosis of supraventricular tachycardia. A detailed ultrasound scan revealed a symmetrically enlarged heart occupying approximately half of the fetal thorax. There were no structural (especially cardiac) abnormalities and no stigmas of chromosomal anomaly. The fetus's size was normal for gestation. Doppler recording from the umbilical artery was also normal (pulsatility index=1.0).

The fetal supraventricular tachycardia was treated by maternal administration of flecainide, initially as an intravenous infusion (2 mg/kg) over 30 minutes followed by 100 mg three times a day orally. Fetal cardiography was used to monitor the fetal heart rate until sinus rhythm was well established. This took 12 hours. Standard and 24 hour maternal electrocardiograms were normal during flecainide treatment. Drug concentrations in the mother were measured twice a week and were in the therapeutic range. The hydrops resolved within 11 days. The oral flecainide was discontinued and there was no recurrence of the supraventricular tachycardia.

The mother was discharged home with a portable Doppler heart rate monitor (Fetal Dopplex, Huntleigh Technology) to use four times daily to exclude a recurrence of the tachycardia. She was followed up in her district hospital with weekly scans to exclude hydrops. There was no recurrence of the arrhythmia and she was admitted at 39 weeks' gestation for induction of labour. She had an uneventful labour and a vaginal delivery of a 3840 g live infant girl with normal Apgar scores. The placenta weighed 1020 g. Cardiological assessment of the infant at birth and at the 6 week follow up visit was normal.

Discussion

Fetal tachyarrhythmias are rare with a reported incidence of one in 10-25 000 pregnancies.¹ This is probably an underestimate since many cases are asymptomatic and undiagnosed. While not all tachyarrhythmias result in fetal hydrops, the high mortality associated with fetal hydrops (20-50%) makes it imperative that these cases are promptly referred for investigation.²

All tachyarrhythmias with associated fetal hydrops require active treatment. It has been suggested that treatment should also be given to those preterm fetuses with a tachyarrhythmia but no signs of fetal hydrops because of the high risk of hydrops developing subsequently (70%), and the lack of a reliable way of predicting the development of fetal hydrops from the type, duration or rate of the arrhythmia.¹ However, with more cases being reported the effectiveness of treatment of tachyarrhythmias in the absence of hydrops is being questioned.^{1 3 4} With Doppler flow studies of the fetal aorta being reported as being useful in the prediction of onset of fetal hydrops,⁵ there would appear to be a place for surveillance and withholding drug treatment in those fetuses with a tachyarrhythmia but no signs of fetal hydrops, remembering

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that all antiarrhythmic drugs have important side effects.

The choice of the optimum drug for treating fetal tachyarrhythmias is controversial. This is reflected by the fact that at least seven different drugs have been reported. Digoxin has been the drug most frequently described but its efficacy, especially in the presence of fetal hydrops, has been seriously questioned.^{1,3} Flecainide, a potent class 1c antiarrhythmic agent, was chosen to treat this patient because of its recently reported high efficacy in those fetuses with severe hydrops.² It is a relatively new antiarrhythmic agent, having been released in the UK in 1983. It has proved to be highly effective against both atrial and ventricular tachyarrhythmias in adults.⁶ In pregnancy it is quick acting with an 80% placental transfer,² which compares favourably with the 40% of digoxin and 10–20% of verapamil.⁴ It is recommended that administration is stopped once sinus rhythm is achieved and the hydrops has resolved.² If the tachyarrhythmia recurs, continued treatment may be required. As with many antiarrhythmic agents it has a negative inotropic effect and hence, in a severely compromised myocardium, either maternal⁶ or fetal,² there is a risk of death. Although there has not been fetal death attributed to the use of flecainide alone, the numbers are too small at this stage to draw any conclusions about its safety. Therefore, at present, it should be reserved for the treatment of supraventricular tachycardias causing fetal hydrops, in those centres with the necessary

paediatric cardiological and obstetric experience. This experience should include the ability to be able to diagnose correctly the arrhythmia, counsel the mother about the potential risks, and monitor both mother and fetus during and after treatment.

Finally, it is not normal practice in most antenatal clinics to record the fetal heart rate; indeed, some professionals may not listen to the fetal heart at each visit although the overall incidence of fetal dysrhythmias is reported as 2% and therefore not that uncommon.⁷ This case serves to emphasise the need to maintain this simple clinical screening method and to refer the case promptly if a fetal arrhythmia is suspected.

We would like to thank Dr L. Allan for her invaluable advice during the management of this patient.

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Family implications of neonatal Gorlin's syndrome

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Abstract

Two very preterm infants (born at 29 and 25 weeks, respectively) were found to have abnormal ribs. Though this was thought unimportant at the time, it was subsequently shown to indicate that some members of their families had a dominantly inherited risk of developing skin cancer and other serious problems.

Case reports

CASE 1

A 22 year old mother with three sons was delivered by emergency caesarean section for breech presentation and placenta praevia. A boy weighing 1200 g was born at 29 weeks' gestation. Serious neonatal illnesses followed, and included idiopathic respiratory distress syndrome (treated with prolonged ventilatory support), tension pneumothorax, bronchopulmonary dysplasia, and episodes of acute circulatory collapse (needing full cardiopulmonary resuscitation). He also had convulsions with intraparenchymal haemorrhage, bleeding from puncture sites as a result of consumptive coagulopathy, acute renal failure (treated by peritoneal dialysis), ileal perforation (requiring laparotomy), and coagulase negative staphylococcal and candida septicaemias. Early routine chest radiographs showed incidentally that the right third and fifth, and the left fifth, ribs were bifid (fig 1). He had a large anterior fontanelle and open posterior fontanelle at 5 weeks of age. The opinion of a geneticist was sought.

The 25 year old father gave a history of dislocated shoulder from birth, examination of which showed Sprengel's deformity. He had pronounced frontal bossing with a head circumference of 62.8 cm (>5 SD above the normal mean). He had hypertelorism with an interpupillary distance of 6.8 cm (>2 SD above the normal mean) and downslanting palpebral fissures. Skull radiographs showed prominent

calcification of the falx cerebri and a pituitary fossa totally bridged by bone, and chest radiographs showed bilateral bifid ribs. The baby's elder brother aged 5 had had a skull radiograph done that showed calcification within the falx cerebri, but his other radiographs showed no abnormality. The 4 year old brother had been diagnosed as having arrested congenital hydrocephalus and chest radiograph confirmed the presence of two bifid ribs. The baby's 21 month old brother's head circumference was 52.8 cm (>2 SD above the normal mean), he had a bossed forehead, and hypertelorism with an interpupillary distance of 5.5 cms (>2 SD above the normal mean). Radiographs showed bifid anterior ends of his left third and fourth ribs, and minor scoliosis of his spine in the mid thoracic region. No members of the family had yet presented with basal cell carcinomata or jaw cysts.

CASE 2

Four and a half months after case 1 had presented, a 31 year old mother was transferred to this hospital with twins and polyhydramnios at 25 weeks' gestation. Fetal ultrasound studies suggested that the second twin had hydrocephalus. The first twin, a girl, was born by normal delivery at 25 weeks' gestation and weighed 825 g. Serious neonatal problems included idiopathic respiratory distress syndrome (treated with ventilator support), tension pneumothorax, and convulsions associated with intraparenchymal haemorrhage. A chest radiograph showed normal ribs. She died on the seventh day of life and postmortem examination was not performed.

The second twin (case 2), also a girl, was stillborn after breech delivery. Intensive resuscitation of the externally normal baby was successful. Idiopathic respiratory distress syndrome was treated with ventilator support but the baby died aged 29 hours. Chest radiographs showed that the right second, third, fourth, and fifth ribs were duplicated in the middle third, and that the left sixth rib was also bifid (fig 2). The scapulas were rotated medially and superiorly suggesting the possibility of Sprengel's deformity. Postmortem examination showed no other deformities and in particular, no evidence of internal hydrocephalus. In view of our recent experience with case 1 the parents were investigated further.

The baby's mother had had five jaw cysts removed since the age of 11 years. On examination she had a head circumference of 56.8 cm (>2 SD above the normal mean), pronounced frontal bossing, and pits in the palms of her hands and feet. She had multiple milia on her forehead, and hypertelorism, with an interpupillary distance of 6.5 cm (>2 SD above the

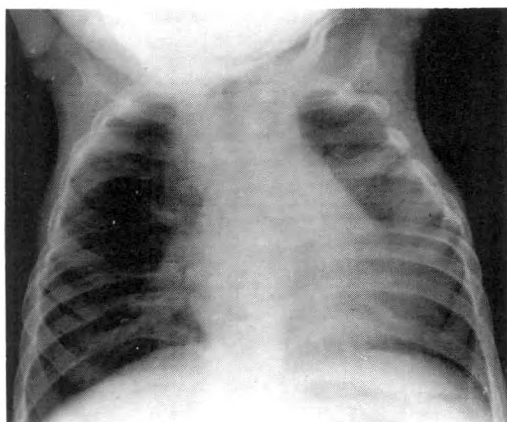


Figure 1 Radiograph of case 1 showing bifid ribs.

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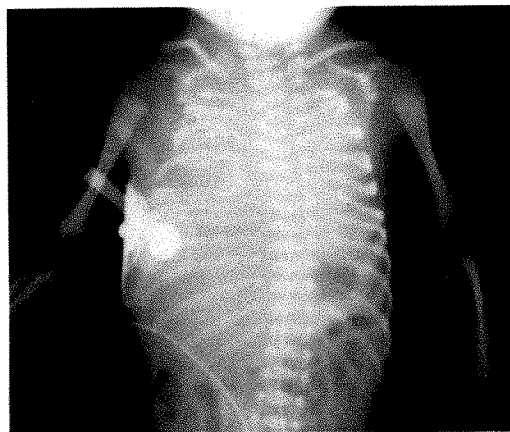


Figure 2 Radiograph of case 2 showing the right second, third, fourth, and fifth ribs duplicated in the middle third, and bifid left sixth rib. Scapulas are rotated medially and superiorly suggesting Sprengel's deformity.

normal mean). There were no signs of basal cell carcinomata. Radiographs showed scoliosis of the spine, a calcified ovarian fibroma, calcification of the falx cerebri, and some minor rib anomalies on chest radiography.

Discussion

The appearance of early calcification of the falx, multiple rib anomalies, and hypertelorism in subjects with macrocephaly segregating in an autosomal dominant manner is highly suggestive of Gorlin's syndrome. Gorlin's syndrome is characterised by the association of

keratocysts of the jaw and multiple basal cell carcinomata.¹ Affected subjects have coarse facies, macrocephaly with frontal bossing, and hypertelorism. They may also have multiple milia on the face and pits in the palms and soles. Skeletal anomalies are usually present, including bifid ribs, vertebral anomalies, calcification of the falx, and bridging of the sella turcica—the last two of which are often present in early childhood. Sprengel's deformity and ovarian fibromata are other common features.

The main complications of asymptomatic basal cell carcinomata (third decade onward) and jaw cysts (second and third decade) necessitate regular (annual) screening with skin examination and orthopantomograms of the jaws. Major and disfiguring surgery is often required if these gene manifestations are not detected at an early stage.

Isolated bifid rib is present in 3–6·2/1000 live births,^{2,3} but in 60% of people with Gorlin's syndrome.¹ The finding of bifid ribs on chest radiographs of the two index cases was of no clinical importance at the time, but had major implications for other affected family members who have a high risk of developing jaw cysts (85%) and basal cell carcinomata (90%).

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Gastroduodenal perforation in preterm babies treated with dexamethasone for bronchopulmonary dysplasia

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Abstract

Three cases of gastroduodenal perforation and one case of ulceration and extreme thinning of the gastric wall occurred in preterm babies treated with dexamethasone for bronchopulmonary dysplasia. This complication of treatment with steroids has not to our knowledge previously been described in preterm infants. Urgent abdominal paracentesis was an essential part of the resuscitation in these cases, and this potentially serious side effect should be considered in all babies treated with steroids.

Treatment with corticosteroids often produces adverse side effects in both adults and children. Whether or not preterm infants differ in susceptibility to some or all of these adverse effects is not yet known, as they have not yet been studied extensively; it is, therefore, important to report all adverse side effects of corticosteroids in this age group so that the risk:benefit ratio can be evaluated and potential adverse effects anticipated.

In this report we describe two cases of gastric perforation, one case of duodenal perforation, and one case of extreme thinning of the stomach wall among preterm babies being treated with dexamethasone for bronchopulmonary dysplasia in the neonatal unit at St James's University Hospital, Leeds, and Huddersfield Royal Infirmary, over a four year period.

Case reports

CASE 1

A male second twin who was born at 30 weeks' gestation weighing 1469 g developed bronchopulmonary dysplasia after severe respiratory distress syndrome complicated by air leaks. On day 18 he developed necrotising enterocolitis, which responded to medical treatment.

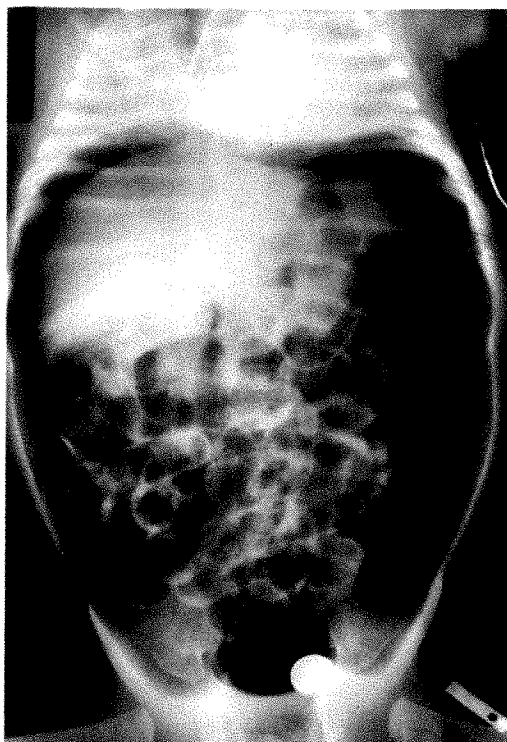
During the ensuing weeks several attempts at extubation were unsuccessful because of chronic lung disease, and a three week course of dexamethasone was started on day 48. The initial dose was 0.6 mg/kg/day, reducing to 0.3 mg/kg/day in the second week, and to 0.15 mg/kg/day in the third week. He was successfully weaned off the ventilator on day 51 and enteral feeding was started the next day. Two days later he had bloodstained nasogastric aspirates, but clotting screen and platelet count were normal. No bleeding sites or bruises were observed elsewhere. He was given cimetidine 20 mg/kg/day for three days and the episode of bleeding stopped spontaneously within 48 hours. On day 69

(the final day of his three week course of dexamethasone) and while receiving alternate bottle and nasogastric feeds of expressed breast milk, he suddenly collapsed with episodes of serious apnoea and bradycardia. He became hypotensive and cyanosed. His abdomen became grossly distended within an hour and an abdominal x ray film showed pneumoperitoneum (figure) but no evidence of necrotising enterocolitis. Immediate resuscitative measures included positive pressure ventilation, and giving atropine, sodium bicarbonate, and a plasma expander. An abdominal drain was inserted, and 60 ml of free gas released from the abdomen, which facilitated mechanical ventilation.

Laparotomy was done within three hours and a perforation was found on the anterior aspect of the lesser curvature of the stomach. There was negligible soiling of the peritoneal cavity and the intestines were healthy. The lesion was oversewn, the baby was weaned off the ventilator within 72 hours, and enteral feeding was restarted. He made an uneventful recovery and was discharged home within a month.

CASE 2

This female infant was the third of triplets born



Case 1: abdominal radiograph (supine) showing tension pneumoperitoneum compressing the thorax.

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at 28 weeks' gestation weighing 895 g. Her neonatal problems included severe respiratory distress syndrome complicated by early pulmonary interstitial emphysema, multiple pneumothoraces, and rapid progression to bronchopulmonary dysplasia. A similar three week course of decreasing doses of dexamethasone was started on day 7. Little progress was made in weaning her from intermittent positive pressure ventilation (IPPV), however, so on day 47 a second course of dexamethasone was started. The dose was similar to the previous one but continued after three weeks with a dose on alternate days of 0.15 mg/kg/day. During this period she was successfully weaned from IPPV into 50% headbox oxygen. On day 90, while taking full nasogastric milk feeds, she passed melaena stools, but this episode resolved spontaneously without any treatment after 48 hours. On day 95 she suddenly collapsed with gross abdominal distension, shock, respiratory arrest, and bradycardia. Fresh blood was aspirated from an indwelling nasogastric tube and abdominal x ray film confirmed the presence of free intraperitoneal gas. Effective ventilation was only achieved after aspiration of 50 ml of free gas from the abdomen.

At laparotomy five hours later a longitudinal perforation was found on the posterior wall of the stomach and the lesion was oversewn. The stomach lining was atrophic and thin. Omeprazole was given immediately after the operation to reduce the output of gastric acid. No further gastrointestinal bleeding occurred and enteral feeding was restarted 10 days after the operation. During her convalescence it became clear that the baby had sustained hypoxic/ischaemic brain injury at the time of the perforation. She died six weeks later of severe bronchopulmonary dysplasia and respiratory failure.

CASE 3

A female infant was born at 27 weeks' gestation weighing 980 g. She developed bronchopulmonary dysplasia after moderate respiratory distress syndrome which was complicated by a left sided pneumothorax. Nasogastric feeding was started on day 2. She was extubated on day 14 and required 28% oxygen. At 3 weeks her oxygen requirements started to increase and by 6 weeks she required 50% oxygen. A chest x ray film confirmed that her bronchopulmonary dysplasia was worsening and a course of decreasing doses of dexamethasone was started at 6 weeks, at an initial dose of 0.6 mg/kg. Within three days her oxygen requirements had fallen to 25%. Nine days after the dexamethasone had been started she became acutely ill with circulatory collapse, and required volume expanders and cardiopulmonary resuscitation. There was pronounced abdominal distension and an abdominal radiograph showed pneumoperitoneum but no evidence of necrotising enterocolitis.

She was transferred to the regional neonatal surgical unit where at laparotomy a duodenal perforation was confirmed. There was minimal peritoneal contamination and the remaining bowel looked healthy. The lesion was oversewn

and the baby was weaned off ventilation after six days. After operation she was given a four week course of cimetidine. She made an uneventful recovery and was discharged home at 3 months of age. She was reviewed at the age of 5 months, and despite a follow up cranial ultrasound scan that showed bilateral periventricular leucomalacia, was progressing normally.

CASE 4

A female infant was born at 24 weeks' gestation weighing 610 g. She had respiratory distress syndrome and required IPPV from birth. Her course was complicated by hypotension and she required inotropic drugs. She had a persistent ductus arteriosus, which was treated with indomethacin, congenital hypothyroidism that required replacement therapy, and bilateral grade II intraventricular haemorrhages. She developed severe bronchopulmonary dysplasia and was treated with intermittent courses of dexamethasone (0.6 mg/kg/day) in an attempt to wean her off the ventilator. The first two courses were interrupted after only a few days because infection was suspected. Dexamethasone was given for a total of 21 days, of which 18 were during the last month of life.

Despite treatment, her pulmonary function continued to deteriorate and she died on day 64 while still receiving steroids. At necropsy two areas of apparently active ulceration were found near the top of the greater curvature of the stomach on the anterior surface, where the wall was extremely thin though there was no obvious perforation.

Discussion

A Medline computer search of papers written in English from 1970–89 inclusive failed to find any reports of gastrointestinal perforation that could have been attributed to the use of corticosteroids in newborns, though it is well documented in adults.^{1–3} Proposed mechanisms include: inhibition of the mucosal cell generative mechanism and the rate of gastric cell turnover^{1,3}; decreased synthesis of antral mucus³; increased susceptibility of intestinal wall to infection¹; thinning of the intestinal wall secondary to depletion of lymphoid patches¹; or synergism with other risk factors such as stress induced ulcer, faecal impaction, or drugs such as theophylline or caffeine that lower the threshold to perforation.^{4–6} Interestingly, there is no reported correlation between the risk of perforation and the dose¹ or the route of administration.³

Stress induced gastric ulceration is an improbable cause of perforation in our cases as none of the babies was receiving IPPV and all were convalescing in the low dependency area of the unit. All were receiving caffeine or aminophylline, but so were most of our very low birthweight babies. Furthermore, a review of admissions to St James's University Hospital during the last 10 years failed to show any other cases of gastroduodenal perforation.

In contrast to many of the reported cases, the anti-inflammatory effect of corticosteroids did

not mask the evolution of abdominal signs in the babies.¹⁻³ The sequence of events was alarmingly rapid and all three babies became moribund within half an hour of the onset of signs. Abdominal distension was so tense that it prevented diaphragmatic movement, and paracentesis with a butterfly needle was life saving. Positive pressure ventilation and vigorous plasma expansion were essential supportive measures during the initial resuscitation period.

The incidence of gastric perforation in pre-term babies receiving dexamethasone in our neonatal unit seems to be in the region of 2% to 3%, in keeping with the finding in adults.¹ The necropsy findings in case 4, however, suggest that there might be cases of active ulceration that go undetected. Two of the babies who had perforations had had an episode of gastrointestinal bleeding that had not been accounted for, although this had stopped days before the perforation occurred.

We suggest that unexplained melaena or bloodstained gastric aspirates in a baby receiving steroids should be regarded as a sign of

impending perforation and possibly as an indication to stop steroids. Whether the risk of this potentially life threatening side effect can be reduced by giving antacids, H₂ receptor blockers, or one of the new generation of hydrogen ion ATPase inhibitors such as omeprazole, needs to be investigated.

We thank Dr M Miller for allowing us to report a case under his care.

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OBSTETRICS FOR PAEDIATRICIANS

Premature labour

Philip J Steer

The survival of premature infants has improved dramatically over the last 20 years, primarily as a result of the development of neonatal intensive care. As papers documenting improved survival appeared, obstetricians began taking more care over the delivery of preterm infants, leading to improved conditions at birth and thus to further improvements in survival.¹ Caesarean section rates of 40% for babies of less than 32 weeks' gestation are now common. The pace of advance has slowed over the last few years, however, and below 26 weeks' gestation or 750 g birth weight or both, major improvements in survival now seem unlikely unless there are fundamental advances in technology. This has lead obstetricians to re-evaluate their strategies with the twin aims of reducing the number of babies that are born who will survive grossly handicapped, and minimising maternal morbidity. In this paper I will survey current obstetric views on aetiology, prevention, and management of preterm labour, including the use of tocolytics and steroids, and speculate briefly on 'the way ahead'.

Aetiology

The aetiology of some preterm labours is not difficult to understand. Cervical incompetence can occur after operations (for example, conisation for cervical intraepithelial neoplasia) or as a result of congenital weakness (for example, after intrauterine exposure to diethylstilboestrol). The equivocal results of trials of cervical cerclage, however, indicate that genuine incompetence is rare, being implicated in less than 5% of cases. Uterine malformations may also give rise to preterm labour, but common ones such as a bicornuate shape are often compatible with term labour, while those such as a thin uterine septum that renders implantation insecure, are rare. The chorionic membranes become inflamed in 50-80% of premature labours, but the incrimination of specific organisms, which would then be susceptible to prophylaxis, has been unsuccessful. Beta haemolytic streptococci commonly cause serious infections in both mother and baby during preterm labour, especially if there is premature rupture of the membranes, but there is no convincing evidence that they cause the labour itself. Studies in the 1970s suggested that *Mycoplasma hominis* and *Ureaplasma urealyticum* might have a role in the aetiology, but this has been difficult to substantiate. Because preterm labour is more common among women of lower socioeconomic status, there is an association with *Chlamydia tracho-*

omatis and *Neisseria gonorrhoeae*, but there is no evidence that either is causative.

Failure to identify specific organisms that have a consistent association with preterm labour has suggested that the primary problem may lie within the immune system of the mother rather than in the nature of the infecting organism. Despite this, immunotherapy of various sorts has so far failed to prevent preterm labour. Disorders of placentation, which cause placental abruption and midtrimester bleeding, are a potent cause of preterm delivery but fortunately are uncommon, so in most cases preterm labour remains 'idiopathic', its specific aetiology unknown. It may be that in many cases it is a response to a hostile intrauterine environment and the trigger of labour lies within the fetus itself (as is probably true of term labour). This would explain why preterm labour is more common among women of lower socioeconomic status, those who smoke, those who are underweight, and those whose babies are born with retarded growth.

Interference with fetal growth associated with poor placental perfusion may occur secondary to maternal disorders such as collagen diseases, heart valve defects, diabetes, and pre-eclampsia. In such cases the risk of spontaneous premature labour is increased, and in addition it is often effected deliberately by the obstetrician to safeguard maternal or fetal health. By keeping it in its unsuitable environment, prolonging the pregnancy may place the baby at greater risk than if it is born. It seems likely that some babies respond to restricted intrauterine nutrition by reducing their growth rate, others by initiating labour, and still others by initiating labour when restricting growth is no longer a sufficient response to impaired placental function. These variations in response may reflect a genetic difference, and could be one reason why women who are born with retarded growth are more likely to have small babies themselves, whereas women who are born preterm have larger than average babies provided they carry to term. Most surveys show that clinicians choose not to give tocolytics in about half their cases of preterm labour because they are concerned about the safety of the intrauterine environment.

Primary prevention

Strategies for the prevention of preterm labour (as opposed to its control, once started) have therefore had to be aimed at improving the intrauterine environment from the beginning of

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pregnancy without the advantage of knowing the precise aetiology in most cases, so they have of necessity been wide ranging. Most studies have been educational, in attempts to reduce high risk behaviour and improve diet, and have provided emotional support from social workers, midwives, and specially trained nurses. Unfortunately most of them have failed to show any significant reduction in the number of preterm births; many wide ranging strategies are costly, and most have now been abandoned. More recently there has been a resurgence of interest in the use of antibiotics. Several small trials have suggested that some benefit may be gained from using antibiotics such as erythromycin, which is active against chlamydia and mycoplasma, as prophylaxis in early pregnancy, and broad spectrum antibiotics such as amoxycillin for preterm rupture of the membranes. These findings need confirmation by larger studies before they can be recommended.

Assessment of risk

The search has therefore continued for treatments that can be applied in a more cost effective way to smaller groups of women who have been identified as being at increased risk of preterm labour. A wide range of techniques of identifying these risks have been published during the last 20 years; careful analysis of a woman's medical and social history at the initial antenatal consultation is of some predictive value, and numerous papers have shown that smoking and a low body mass index (weight (kg)/height (m)²) indicate the largest risk. Unfortunately it is difficult to persuade those women who are most at risk to give up smoking, and underweight women are twice as likely as women of normal weight to eat poorly in pregnancy and fail to gain weight. Social factors have some influence, but are difficult to categorise and rarely generalisable. It used to be thought that pregnant women should give up work outside the home at 28 weeks, and that failing to do so could increase the risk of preterm labour. Most studies suggest, however, that women who continue in employment fare better than women who stay at home, the only exception being those engaged in heavy manual work.

The single most important predictor in multiparous women is the birth weight and gestational age at delivery of the previous baby. Chng *et al*, however, has shown that these are usually ignored by midwives and doctors at 'booking' clinics.² This may be partly because previous birth weights are usually recorded from the mother's recall, in pounds and ounces, whereas most of us are now calibrated to normal values in kilograms. More complex screening systems, such as those of Hobel *et al* in the USA,³ have been widely used but recent evaluations have shown them to be of no practical value.⁴

Disillusionment with historical methods has led to experiments with strategies such as the recording of preterm uterine activity with external tocodynamometers, and regular assessment of cervical compliance and dilatation by

digital examination. The latter is currently routine in many European countries including France, Belgium, and Spain. While there is a reasonable correlation between increased frequency of Braxton-Hicks contractions or an inappropriately dilated cervix and preterm delivery, up to half the women who have abnormalities of these measures will carry to term, and the techniques carry a substantial penalty in terms of cost, time, and discomfort for pregnant women. Even more importantly, they are only of real value if they allow the application of an effective treatment; currently, such treatment does not exist.

Diagnosis of preterm labour

The diagnosis of preterm labour is difficult. Placebo controlled studies of tocolytics have shown that 70% of women in apparent preterm labour and allocated to receive placebo go on to deliver at term, and therefore were not truly in labour when the diagnosis was made. The only sure way to diagnose labour remains the demonstration of progressive cervical dilatation. Careful cervical assessment should be made on all women admitted to hospital with abdominal pain, vaginal discharge or bleeding, or any other symptom suggestive of preterm labour. The assessment should be repeated if there is any sign that labour might be progressing, and again before discharge from hospital. Such examinations are often omitted on the grounds that they might provoke labour or cause infection. There is no evidence that any number of examinations when the membranes are intact, and up to three when they are ruptured, have any such effect provided that appropriate aseptic technique is used. On the other hand, there is good evidence that knowledge that delivery is imminent, thus allowing choice of an appropriate place for delivery and the attendance of paediatricians at the time of delivery, improves the chances of survival. It has been suggested that fetal breathing movements, which usually disappear in labour, might be a useful diagnostic variable. Lack of appropriate ultrasound equipment and trained personnel on labour wards out of hours have, however, prevented this from being tested in realistic clinical trials.

Tocolysis and corticosteroids

Tocolytic therapy for the prophylaxis and suppression of preterm labour became popular in the 1970s when some tocolytics such as ritodrine were massively promoted and achieved substantial 'market penetration'. Papers have now been published about at least 18 different tocolytics ranging from β sympathomimetics such as ritodrine, to prostaglandin synthetase inhibitors such as indomethacin, calcium channel blockers such as nifedipine, and direct muscle relaxants such as magnesium sulphate. While most of them can achieve suppression of uterine contractions for a limited period (usually 48 to 72 hours), which is long enough to allow corticosteroids to promote release of fetal lung surfactant, and the preparation of appropriate circumstances for delivery, none of the currently

available evidence suggests there is any improvement in neonatal survival from long term treatment. The risk to the mother of serious complications such as pulmonary oedema and hyperglycaemia is such that Kierse *et al.*, after an extensive review of evidence from randomised controlled trials, recently recommended that long term treatment with any contraction suppressing agent should not be used outside clinical trials.⁵ Such a conclusion is in sharp contrast to that for corticosteroids, which are of proved benefit in all racial groups and in fetuses of both sexes, from at least 26 weeks (and possibly before) to 32 weeks' gestation.

Cervical cerclage

Cervical cerclage (putting a 'stitch', usually branded polyester (Mersilene) tape, around the cervix) has also waxed and waned in popularity during the last 20 years. Most obstetricians use the simple MacDonald procedure, in which the knot remains exposed and the suture can be removed in late pregnancy, rather than the 'Shirodkar' suture, in which there is extensive dissection of the bladder from the cervix, a buried knot, and usually caesarean delivery. It now seems that it may be of benefit where there is evidence of true cervical incompetence (for example, after previous traumatic termination of pregnancy, or cervical surgery for neoplasia), although the outcome is changed in only about 5% of those who undergo the procedure. The realisation that in cases of previously otherwise unexplained preterm labour there is no demonstrable benefit has led to a pronounced decline in the use of cerclage in such cases.

Preterm premature rupture of the membranes

The increasing success of neonatal intensive care in the 1970s led to an interventionist approach in the management of preterm rupture of the membranes, treatment with corticosteroids being followed by elective delivery after 48–72 hours. Despite the confirmed value of corticosteroids, however, hyaline membrane disease remains a major problem with early delivery, and the balance has once again swung back to conservative management. In the USA, amniocentesis is often used to detect amnionitis, but evidence of its value is lacking and it has not yet been generally accepted in the UK. This is particularly true outside teaching hospitals where there are no facilities for scanning out of hours, amniocentesis, or Gram staining and immediate culture of samples. A current worry is that the lungs of fetuses in which the liquor has been profoundly reduced for more than three weeks may fail to develop properly; this is a particular problem when the membranes rupture before 24 weeks when early delivery is not a reasonable option. In such cases termination of pregnancy may be a preferable course of action.

Management of very preterm labour

The management of established preterm labour (strictly, a 'threatened miscarriage') between 22 and 28 weeks' gestation is a particular problem.

Important decisions have to be made that centre on the viability of the infant. A recent national survey has shown that over 80% of obstetricians in this country do not favour surgical intervention (caesarean section) on fetal grounds alone at less than 26 weeks' gestation. This decision depends on accurate dating of the pregnancy, however, and preterm labour is over-represented in women who have failed to attend for antenatal care. In addition, most obstetricians would not be keen to intervene if the fetus weighed less than 650 g, principally because it is usually necessary to resort to a classical caesarean section for these very small babies, as the lower segment of the uterus is not sufficiently formed to allow the usual lower segment approach. Classical caesarean section is associated with substantial maternal morbidity, particularly in relation to subsequent pregnancies in which uterine rupture can be a catastrophic complication and repeat caesarean section is mandatory. A third of babies below 28 weeks' gestation present by the breech, so determining presentation is also vital. Estimation of fetal size and presentation, therefore, remain the cornerstone of appropriate management. Unfortunately these require good ultrasound equipment and obstetricians who are skilled ultrasonographers; currently these are available for 168 hours a week in only a minority of British maternity units.

Fetal monitoring and resuscitation

It is now well established that if fetuses of 26 to 36 weeks' gestation are monitored with continuous cardiotocography and fetal blood sampling, the criteria for normality are similar to those for term fetuses. The differences are that very preterm fetuses have less baseline variability in fetal heart rate, the normal quiet/active sleep cycling is often absent, and there are often small (<40 beats/minute), short (<20 seconds), decelerations that do not seem to have sinister implications. Normal ranges of fetal blood gas and pH values are similar to those at term. Whether babies of less than 26 weeks' gestation or with an estimated weight of less than 650 g should have continuous fetal monitoring is controversial. One view is that if intervention on fetal grounds is not contemplated, then the fetus should not be monitored as it may upset the mother and staff if it becomes abnormal and there is no intervention. Those who believe this also advocate the view that if the fetus has been 'written off' in this way by the obstetrician, the paediatrician should not be asked to attend the delivery. They suggest that if the paediatrician attends, and sees signs of life even in a very tiny baby, resuscitation is obligatory.

A second view is that a senior paediatrician should attend all such deliveries, and then make an objective decision as to whether the baby should be actively supported or not. He may be helped in such a decision by knowledge of the fetal heart rate pattern, and even occasionally by measurement of blood gases and pH from the umbilical cord. An extension of this approach is that the baby should be resuscitated and stabilised, after which a decision to continue or

remove support can be made. This course of action, however, runs the risk that the 'window of opportunity' during which nature can be allowed to take its course may pass. In the light of finite resources and the need to use those available most effectively, obstetricians and paediatricians must coordinate their efforts closely if this issue is to be resolved.

Mode of delivery of a preterm infant

The mode of delivery of a preterm infant has been a contentious issue during the 1980s. A recent survey showed that it is now widely accepted that—for the baby being born head first—there is no need to do a routine forceps or caesarean section, whatever the gestation, unless there is a specific fetal indication such as a severely abnormal heart rate pattern or acidosis. At one time it was widely believed that because preterm infants have a much higher incidence of low Apgar scores at birth, this reflected 'birth asphyxia' and thus labour was intrinsically more stressful for the preterm than the term infant. Two factors have changed this view. Firstly, it is now appreciated that low Apgar scores do not necessarily indicate 'birth asphyxia' if biochemical disturbance including hypoxia and acidosis is meant. Half of all mature babies born with low Apgar scores do not have acidosis, and this proportion is even greater among preterm infants who usually have cord blood oxygen tension and pH similar to those of term babies at birth.⁶ Secondly, we now know that the reason for the increased incidence of low Apgar scores in preterm babies is usually immaturity such that respiratory effort, tone, and reflex irritability are less well developed than in the term baby. This is an effect of gestational age and is not produced by impaired placental gas exchange.

The picture in relation to the preterm fetus in the breech position is not so clear cut. A substantial number of retrospective studies have reported lower mortality and morbidity when preterm fetuses in the breech position were delivered by caesarean section. Unfortunately the studies were all retrospective and uncontrolled, and it is inappropriate to compare a planned caesarean section with senior obstetric and paediatric staff present with an unexpected vaginal delivery supervised by less experienced staff in a cold accident and emergency department. For the last 20 months a multicentre randomised controlled trial of the mode of delivery of the preterm (26–32 weeks' gestation) breech has been underway in 22 centres in the UK. Recruitment has, however, been slow, with only 10% of eligible cases being randomised, which seems to reflect obstetricians' reluctance

to abandon individualised management even in the presence of uncertainty. The need for the trial has been emphasised by the finding that so far two babies allocated to vaginal delivery remained undelivered until after 32 weeks, and a further two were in cephalic presentation at delivery.

In utero transfer

The benefit of in utero transfer for the baby is well attested. The risks to the mother of delaying delivery to allow transfer are sometimes less well appreciated. This is particularly true of those with fulminating pre-eclampsia or eclampsia; during the last 15 years hypertensive disorders of pregnancy have been the leading cause of maternal mortality. The onset of eclampsia indicates that immediate delivery is necessary to safeguard maternal health; transfer by ambulance of women at risk of fitting is too dangerous to be justified. In a recent national survey of triplet pregnancies, the case was reported of a woman whose delivery was delayed for some days until a neonatal unit able to take her babies was found; after delivery she died from the complications of her pre-eclampsia.

The way ahead

It seems unlikely, given the complexity of the problem, that there will be any sudden 'break-throughs' in the prevention of preterm labour. Work must continue to elucidate the various causes in the hope of finding specific treatments for specific causes. In the meantime we must attempt to improve our management by properly designed controlled trials such as those that have confirmed the efficacy of treatment with corticosteroids. The greatest practical benefits in the short term are likely to flow from the increasing involvement of senior obstetricians, and the provision of adequate ultrasound and fetal monitoring facilities on all labour wards.

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PERINATAL LESSONS FROM THE PAST

Dr Nils Rosen (1706-1773): the father of paediatrics in Sweden

P M Dunn

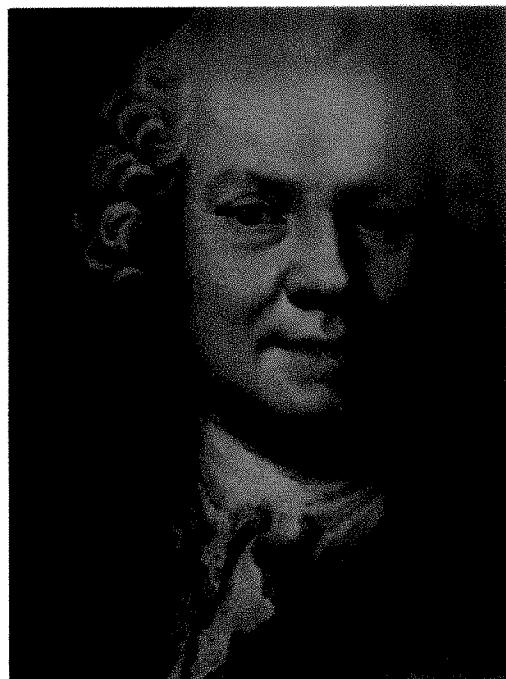
Nils Rosen was born in 1706, his father being a chaplain in the army of Charles XII. After schooling in Gothenburg, he studied medicine at the University of Lund from 1722-4 before taking up a tutorship in Stockholm. In 1727 he was appointed Adjunct by the University of Uppsala but spent the next three years travelling and studying on the continent, first in Germany and Switzerland, and then in Holland where he came under the influence of Dr Boerhaave of Leiden. He obtained an MD at the University of Harderwijk before returning to take up his teaching post in Uppsala in 1731. Nine years later he succeeded to the Chair of Medicine, becoming responsible for anatomy, physiology, pathology, therapeutics, chemistry and for directing the University Hospital. A second chair in theoretic and practical medicine was filled in 1741 by Carl Linné who became responsible for botany, materia medica, dietetics and semiotics, and Director of the Botanical Gardens.

Rosen was an excellent clinical teacher with a gift for simplifying complicated subjects. He pioneered the teaching of applied anatomy and bedside instruction in Sweden and did a great deal to promote child health and to introduce a better understanding of the needs of children among physicians and mothers.

He was a good correspondent but did not publish a great deal. His major work *The Diseases of Children and their Remedies* was first published in Sweden in 1764 and was later translated and published in English in 1776.¹ It is from this work that the extracts that follow were taken. His book abounds with excellent advice on how to choose a good nurse, on breast feeding, on the dangers of overtight swaddling, and on other aspects of infant management. This, for example, was his advice on when to wet nurse an infant:

'The business of a nurse is to suckle the child whenever it is hungry or dry, but not by any means so often as it shrieks or cries . . . she may easily perceive when it wants to be suckled: (1) From the time it has gone without suck. (2) If it fixes its eyes on the nurse, and they seem as if it were to follow her wherever she goes. (3) If joy sparkles from the child's eyes, when she opens her breasts. (4) By the child sucking her finger on its being put into its mouth'.

His chapter on thrush, a condition which was very prevalent at that time, is also of interest:



Nils Rosen von Rosenstein, 1706-1773.

'On the aphthae or thrush

This is attended with many bad symptoms, and often endangers the child's life; for besides that children shriek day and night on account of the pain, they are unable to suck, and consequently suffer by both hunger and thirst; if at this time they suck, the nurse's nipples commonly will be excoriated and sore: if the thrush extends to the throat, they have a difficulty of swallowing; if it descends to the stomach, they will have many reachings and hiccough; and if it extends still further down to the bowels, the chyle will be prevented from entering the lacteal vessels, and the blood is carried off by a diarrhoea: if this continues long the child must die for want of nourishment.

The thrush is commonly of a white . . . colour . . . That which appears first upon the lips, gums, tongue, inside of the cheeks, palate, uvula and tonsils is the easiest to cure. It is very difficult when it descends to the fauces, stomach and intestines. It is still more dangerous if it has reached the aspera arteria and the lungs . . . The thrush in the mouth is the most common kind, and may generally be prevented by the nurse taking care to keep the child's

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mouth clean, which should be examined every day . . .'

Perhaps, though, Rosen's most interesting chapter is that which deals with congenital syphilis.

'On the cure of children born with the venereal disease, or infected with it by nurses

When the parents have a venereal disease, it is very natural that the children they beget will be born with the same. But as the poison (virus venereum) at the time of conception may either be active, vigilant and acute; or inactive, blunt, and dead as it were, its effect on the child will also be different. If the poison is active at that time, the child in the womb will generally lose its life; therefore we find such unhappy mothers often miscarry or are brought to bed with dead children; and in case they be brought into the world still alive, they nevertheless will be found with sores and other evident signs of the venereal disease. Should the poison at such a time be less active, the child may be born with a healthy appearance, but after some time, its body will break out with sores and boils. But when the poison at the time of conception lies dormant, either naturally, or by some remedies which the parents have used, and by which it has not been quite exterminated but only weakened, the child will scarce ever get any venereal disease . . . Such children grow tender and weak, as also their offspring, from generation to generation . . . This is the reason that of several children of the same parents, which are in this unhappy condition, some enjoy a perfect health, whilst both the body and the senses of the others are affected'. . .

In the same manner in which a nurse can infect a child, a child also born with the venereal disease may infect its nurse: and here one thing is to be observed, which seldom fails, namely, that the parts which are touched first by the contagion will always suffer first. Therefore when a child is infected by the nurse, it then gets corroding sores in its mouth, but chiefly in the fauces, and the glands of the jaws and in the throat swell and grow hard. If the nurse has gotten the contagion from the child, she will first get the corroding sores on her breasts, and the glands in her armpits grow swelled and indurated . . .

The venereal disease is in general curable if it is not suffered to grow too inveterate; for the shorter time it has been in the body, the more easily will it be removed. The cure is more difficult when the bones are already affected.

However, the disease is seldom quite eradicated, because the patient grows tired, and breaks off the cure as soon as the pains have ceased, and the body appears clean. From thence it happens that they get relapses, or grow indisposed for all their life-time . . .

I will now advance to the cure itself, and first

mention how to relieve a woman who is found to be infected with a venereal disease during the time she is big with child, which consequently must likewise be infected. In such unfortunate circumstances there is no time to lose, but a quick relief is required; for if the cure be deferred till she is delivered, the foetus will in the meantime die, and at least be brought into the world half rotten, or with little life. The mother is during that time subject to miscarry . . . Therefore such a patient ought immediately to be well prepared, and with great caution use the mercurial ointments. . .

When a child is born with this disease, and is still of a tolerable lively appearance, we have hopes to cure it by the mother's using the mercurial ointment, and the child sucking her during the time. If the mother be too weak, we are obliged to procure the child a nurse who will go through the same cure. It is advisable to make her acquainted with all the circumstances before-hand, in order that the parents may avoid a disagreeable prosecution, as it once happened in France.

But as the mother's or nurse's breast and nipples commonly grow so sore and swelled on suckling such a child, that the milk will not flow, physicians have been obliged to think of another method, which perhaps is the safest; a goat must be well chased and cleared of hair, and rubbed with the mercurial ointment in the same manner as it is done to people; the child must live on her milk during the time till it is cured. Mr D'Aumont, professor in Valence, cured a child in this manner within 35 days . . .'

These extracts reveal a remarkably good understanding both of the method of transmission of syphilis and its treatment. The final section is of particular interest because of its use of goats' milk as a therapeutic vehicle and also because it discusses the need for counselling and consent as a defence against medicolegal prosecution—a modern touch!

In 1739 Rosen was elected to the newly formed Royal Academy of Science and was made President in 1746 and in 1772. In 1734 he was appointed physician to King Fedrik I and for his many services to the royal family was ennobled as Rosen von Rosenstein in 1746 and made a Knight of the Polar Star. He had married Anna Christina Hermansson in 1734 and they had three children, one of whom sadly died after variolation at the age of 4. Rosen's own health was poor, mainly as a result of rheumatoid arthritis and he resigned his post and retired to Stockholm at the age of 51 in 1757. His health remained poor and he died during a visit to Uppsala in 1773.

¹ Rosen von Rosenstein N. *The diseases of children and their remedies*. Translated by A Sparrman. London: T Cadell, 1776.

ARCHIVES OF DISEASE IN CHILDHOOD

The Journal of the British Paediatric Association

Annotations

Use of antiepileptic drugs in childhood epilepsy

Attitudes to the treatment of childhood epilepsy with antiepileptic drugs have been changing during the past decade. It is now widely accepted that epilepsy in children is very different from epilepsy in adults and that studies of drug treatment in adults are not necessarily directly applicable to children.¹ Before starting treatment with these drugs in a child it is important to establish a firm diagnosis of epilepsy, to identify the type of epilepsy or epileptic syndrome which is present, as far as is feasible, and to categorise the seizure type or types in the individual patient.

The epilepsies or epileptic syndromes may broadly be divided into those with no established aetiology but which are probably of genetic origin (idiopathic or primary) and those with a known aetiology (symptomatic or secondary) in which a brain lesion is suspected or can be demonstrated. A further subdivision is into those epilepsies with generalised seizures (generalised epilepsies) and those with partial seizures (partial or localisation related epilepsies).² It should be remembered, however, that similar seizures may occur in different syndromes and that some syndromes are characterised by multiple seizure types. While some epileptic syndromes are highly specific and a few have recently been shown to have chromosomal markers, many represent broad concepts only.³ Furthermore, not all patients fit into the described syndromes. Nevertheless, this approach to childhood epilepsy had undoubtedly improved the management of the condition in recent years and has led to more rational use of the available drugs.

The drug treatment of epilepsy always needs to be considered on a risk versus benefit basis as no drug is free of risk, although modern drugs are superior in this respect especially where cognition and behaviour are concerned.⁴ Furthermore, the need to treat at all should be debated as, in many of the primary epilepsies, attacks are infrequent anyway and the outcome is usually excellent.^{5,6} Two common disorders of this kind are benign partial epilepsy with rolandic (centrotemporal) spikes and febrile convulsions. In the former, up to one quarter of the patients have one seizure only with one half having fewer than five seizures.⁷ In the case of febrile convulsions, the therapeutic pendulum has swung strongly against pharmacological prophylaxis during the past decade, to be replaced by intermittent forms of treatment using diazepam rectally.⁸ Single seizures are also a feature of some of the primary generalised epilepsies, notably when an idiopathic tonic-clonic seizure occurs in an otherwise normal child with a normal electroencephalogram. In such a situation, recurrences may not be

seen in over half of the cases.^{9,10} However, the observations of Reynolds on untreated epilepsy should be borne in mind.¹¹ His collaborative study has demonstrated, in children as in adults, a significant and important relationship between the number of seizures before treatment and the ultimate prognosis.¹² When a second attack follows quickly on the first (in a month or less), early institution of treatment is mandatory and may influence the long term outcome.

If drug treatment of epilepsy is started, it should be withdrawn as early as is feasible. In children, remission rates of over 75% have been consistently reported in those who have been seizure free for two years.^{13,14} The benign nature of much of childhood epilepsy needs to be more widely recognised. The long term prognosis for children with epilepsy is nearly always closely related to the type of epileptic syndrome which is present and ultimately to the aetiology. The presence of structural brain abnormality, mental and developmental handicaps, and certain seizure types are associated with a worse prognosis.

With refinements in diagnosis and with the availability of accurate monitoring of drug concentrations has come the realisation that the treatment of epilepsy with a single drug (monotherapy) is superior to the use of multiple drug treatment. It is now clear that polytherapy was responsible for much unnecessary and avoidable drug toxicity in the past. It also led to ineffective treatment because of drug interactions and to difficulties in evaluating the effects of individual drugs. Another feature of multiple drug treatment is a poor risk-benefit ratio that is revealed when the efficacy of drug combinations is critically assessed.¹⁵ In the treatment of newly diagnosed patients with epilepsy, whether adults or children, the evidence now strongly supports the value of antiepileptic drug monotherapy and approximately 75% of patients can be expected to enter prolonged remissions on such a regime.¹² If the drug chosen initially proves ineffective at the highest tolerated dosage, a second drug should be tried alone. Drug combinations may be justified in patients with resistant disease, although such combinations are rarely successful. An exception is the combination of ethosuximide and sodium valproate for resistant childhood absence epilepsy (petit mal).¹⁶ Adjunctive or 'add-on' treatment with drugs such as clobazam or acetazolamide may sometimes be effective in controlling intractable seizures in certain epileptic syndromes.¹⁷

Because young children tend to metabolise antiepileptic drugs more rapidly than older individuals, they may require

higher dosage in relation to body weight.¹ Determining blood concentrations of drugs is important in children but it should be remembered that the so called 'therapeutic range' is a relative concept and should not be applied blindly.¹⁸ As much drug as is needed but as little as is necessary to control the seizures should be given,⁶ polytherapy should be avoided, and drug concentration monitoring used widely. An added inducement to use low doses where possible is that, in patients on monotherapy with various drugs, the effects on memory, attention and concentration, perception and decision making, are twice as great at a high serum concentration as compared with a low serum concentration in the same patient.¹⁹

Although factors such as seizure type and the underlying aetiology of the epilepsy influence prognosis, the influence of choice of antiepileptic drug on the prognosis is less clear. Leaving aside childhood absence epilepsy where ethosuximide and/or sodium valproate are uniquely effective, controlled studies to determine the relative efficacy of four major antiepileptic drugs, that is, phenobarbitone, phenytoin, carbamazepine, and sodium valproate, utilised as monotherapy, showed no significant differences in efficacy in either adults or children, regardless of which method of patient assessment was employed.¹² However, bearing in mind the known effects on cognition and behaviour of the barbiturates (including primidone), phenytoin and the benzodiazepines,¹⁹ paediatricians will opt to use carbamazepine and sodium valproate as their drugs of first choice. Although carbamazepine probably has only a minimal adverse effect in these respects, sodium valproate may affect behaviour, apparently as an idiosyncratic effect, and can also impair cognition.²⁰

A more worrying problem with sodium valproate is the possibility of fatal hepatotoxicity developing as an idiosyncratic reaction, usually within the first 90 days of treatment. It should be remembered that, although drug related rises in serum enzyme activities may be detected in up to 44% of patients receiving valproate treatment,²¹ these rises are not accompanied by clinical symptoms or by abnormalities in the liver's synthetic functions (for example, prothrombin time). These laboratory abnormalities resolve with dosage reduction or with stopping the drug. The incidence of fatal hepatotoxicity is not evenly distributed among the patient population. Very young patients (0–2 years) on polytherapy with antiepileptic drugs and who have other medical conditions in addition to epilepsy are disproportionately vulnerable to fatal hepatic failure.²² This is usually attributed to an aberration in the metabolism of the drug and may, in some cases, be associated with an inborn metabolic defect.²³ Sodium valproate prophylaxis for febrile convulsions is, therefore, not really an option under 2 years of age, except in exceptional circumstances, and short term phenobarbitone treatment is a wiser choice in the rare instances when continuous treatment is deemed necessary.⁸

The good news about sodium valproate treatment is that the incidence of fatal hepatotoxicity from the drug is declining.²⁴ This has been ascribed to the increasing use of the drug as monotherapy and the limitation of its use to low risk patients (over 2 years). Sodium valproate should not be given in a polytherapy regime to those under 3 years of age, it should be avoided in patients with pre-existing liver disease or with a family history of such disease, and salicylates should not be given to a patient on sodium valproate. Fasting should be avoided in such patients who have an intercurrent illness, and immediate withdrawal of the drug is mandatory if hepatotoxicity is suspected. Prodromal signs of this are nausea, vomiting, anorexia, lethargy, and also a sudden loss of seizure control or even an episode of status epilepticus.²⁵ One stage prothrombin time and fibrinogen concentrations are more sensitive than other

indices of liver function in detecting hepatic compromise. Although valproate hepatotoxicity is rare, it may occur at any age and vigilance is required to detect its early onset.

Despite these caveats about sodium valproate, both it and carbamazepine are widely used today in the treatment of childhood epilepsy. It is worth entering a caveat here about carbamazepine also which, apart from its annoying propensity to cause a generalised rash just when its anticonvulsant properties are most needed, may also exacerbate seizures, especially when used to treat the multiple seizure types of the Lennox-Gastaut syndrome or absence seizures of various kinds.²⁶ Carbamazepine, in the writer's experience, has been an outstanding and safe antiepileptic drug for treating childhood epilepsy over nearly three decades. It is particularly effective in simple and complex partial seizures. Sodium valproate is usually very effective in generalised convulsive and non-convulsive seizures, especially when they are due to a primary or idiopathic epileptic syndrome and are associated with 3 Hz spike wave discharges on electroencephalography.

These are several new antiepileptic drugs in the course of development²⁷ and two have arrived recently on the commercial market. Both of these have been developed as a result of a logical pharmacological approach to treatment, which has attempted to find drugs which either enhance synaptic inhibition or reduce excitatory neurotransmission. The former is largely mediated by γ -aminobutyric acid (GABA) and γ -vinyl- γ -aminobutyric acid (vigabatrin) is a synthetic derivative of GABA which acts as an irreversible inhibitor of GABA transaminase, the enzyme responsible for the breakdown of GABA. Its action results in an increase in inhibitory neurotransmitter at the synapse. The drug is not bound to protein, is excreted largely unchanged in the urine, and monitoring of serum concentrations is not advised. Vigabatrin has been used so far as adjunctive treatment for chronic and intractable seizures in adults and, in these, about half of the patients treated have shown a reduction in seizure frequency.²⁸ Partial seizures with secondary generalisation have shown the best response. Thus far, experience in children is limited and confined to intractable cases but uncontrolled partial seizures seem to respond best and myoclonic seizures may also show a response, especially the intractable seizures of West's syndrome (infantile spasms) due to tuberous sclerosis.²⁹ Although vacuolar changes in myelin were reported in some animals given vigabatrin, clinical effects resulting from something of that nature have never been reported in man. Nevertheless, vigilance for evidence of chronic toxicity is required, especially in children. The drug will clearly have an important role in the treatment of resistant epilepsy in the future and may begin to be used more widely as first line rather than adjunctive treatment.

The other new antiepileptic drug, lamotrigine, is designed to act by inhibiting the release of excitatory amino acids, principally glutamate, at the synapse. It is recommended for use at present as adjunctive treatment for partial seizures and generalised tonic-clonic seizures that are not satisfactorily controlled by other antiepileptic drugs.³⁰ These older drugs may increase its metabolism by liver enzyme induction, although sodium valproate reduces it. It seems to be relatively non-toxic although rashes may occur. Experience in childhood is limited and a multicentre trial of the drug as adjunctive treatment for resistant epilepsy is still in progress in the UK.

As was emphasised earlier, epilepsy in childhood is quite a different problem from epilepsy in adults and its treatment with or without drugs is influenced by many factors unique to that period of life. The British Paediatric Association, in 1988, emphasised the importance of better control of epilepsy among the priorities for child health in the future.³¹

Interest in and understanding of epilepsy have never been greater than at present and, with the rapid development of knowledge of the molecular biology and neurochemical mechanisms underlying epilepsy, it is likely that research will provide more effective and safer drugs in the near future.

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Transoesophageal echocardiography: a new diagnostic method in paediatric cardiology

Over the past decade cardiac ultrasound techniques have revolutionised the practice of paediatric cardiology. Transthoracic cross sectional imaging allows for an accurate and non-invasive assessment of intracardiac morphology in the vast majority of children. Doppler ultrasound techniques provide a detailed insight into the related haemodynamic changes of congenital cardiac lesions.

Transoesophageal echocardiography has become an established diagnostic and monitoring technique in adult cardiology.¹ An ultrasound transducer, mounted at the tip of a flexible endoscope, is introduced into the oesophagus and echocardiographic studies can be performed without interference of either the thoracic cage or lung tissue. This produces high quality images in every patient studied. Some two years ago, miniaturised transoesophageal probes were developed,² which allow studies to be carried out in even small children.^{3,4} However, what are the advantages and what are the relative contributions of transoesophageal studies in children with congenital heart disease? Do we need a further diagnostic and monitoring technique?

Over a two year period more than 240 transoesophageal studies have been performed at the Sophia Childrens Hospital, Rotterdam, the Netherlands and the Royal Hospital for Sick Children, Edinburgh, Scotland. The

results of these studies were reviewed to determine the role of paediatric transoesophageal studies in different clinical settings. All transoesophageal studies were carried out under either general anaesthesia (given in the majority of cases for either cardiac catheterisation or cardiac surgery) or heavy sedation. Antibiotic endocarditis prophylaxis was not administered in any patient, and no episode of bacterial endocarditis was observed. Complications were encountered in three children (1.2%). These included arrhythmias in two. Oesophageal bleeding was encountered in only one patient. No death occurred.

Primary diagnosis of congenital heart disease

When compared with transthoracic echocardiographic studies, the transoesophageal ultrasound approach provides a more detailed evaluation of the morphology of the atrial chambers. The visualisation of both atrial appendages, for the first time, allows the direct diagnosis of atrial situs⁵ and the definite preoperative documentation of juxtaposed atrial appendages.⁶ The morphology and integrity of the atrial septum is frequently better assessed by transoesophageal studies. Superiorly located defects, such as sinus venosus atrial septal defects, can be visualised in much greater

detail. Multiple atrial septal defects can be identified with ease. In addition, the borders of any defect can clearly be defined, as can be the presence of any tissue flap of the oval fossa that may partially cover the defect. These detailed insights to be obtained by transoesophageal studies may be anticipated to have major implications on a refined patient selection for transcatheter atrial septal defect closure.

Anomalies of either the systemic or pulmonary venous return are much more readily diagnosed by transoesophageal than by transthoracic echocardiographic studies.⁷ The individual sites of connection of all four pulmonary veins can be documented in 93% of the cases, thus providing a most sensitive tool in the preoperative exclusion of anomalous pulmonary venous connections. When compared with angiocardiology, the technique provides additional morphological information on the site of venous connections relative to the atrial septum. Thus in children with this range of lesions transoesophageal studies are highly beneficial in the preoperative diagnosis. In older children with complex congenital heart disease, involving the atrioventricular junction of the heart, transoesophageal studies constitute an important adjunct in the preoperative diagnosis.⁸ Major contributions include the exclusion of chordal straddling and the definition of the valvar and subvalvar anatomy (figure). Transoesophageal studies should be considered to be essential in all children in whom a septation procedure is considered.

In children with their generally good transthoracic ultrasound windows, relatively little additional information is gained by transoesophageal studies on either the ventricular chambers, the ventriculoarterial junction, or the great arteries. The only exception is a more detailed assessment of the morphology of the range of lesions producing left ventricular outflow obstruction in childhood.

Monitoring of surgery and interventional catheterisation

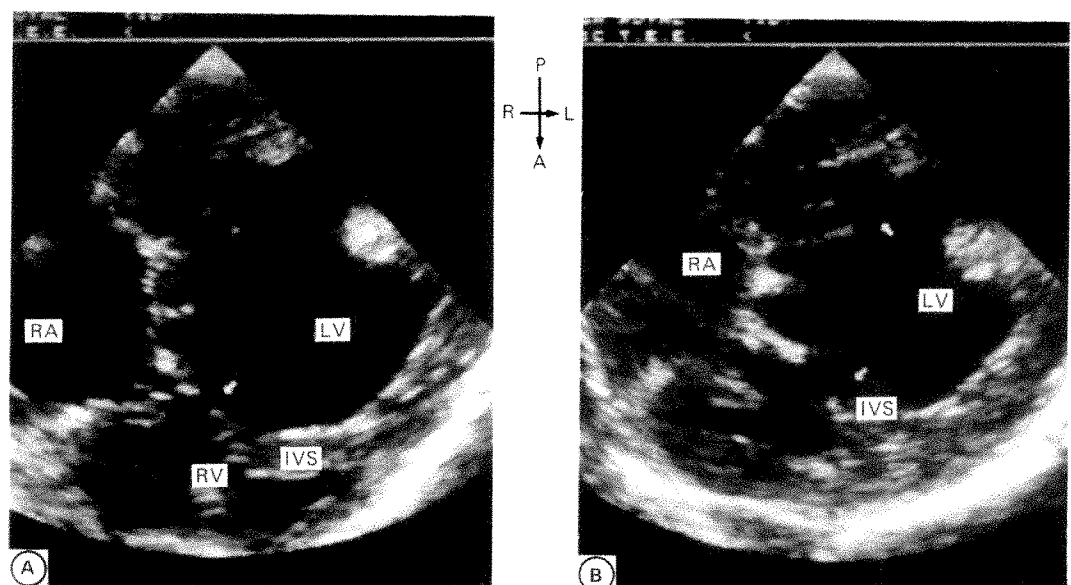
Transoesophageal studies can be used effectively in the monitoring of cardiac operations. The surgical results can

be documented and the majority of residual lesions identified immediately.⁹ However, intraoperative oesophageal studies are limited when compared with epicardial ultrasound studies,¹⁰ which provide resolution imaging and an unlimited range of in planes. The major implications of transoesophageal studies would appear to lie in the diagnosis and management of early postoperative complications, when preoperative imaging is frequently impossible.

During interventional cardiac catheterisation transoesophageal studies proved to be a versatile real time in and monitoring technique. Studies can be performed out either interference or prolongation of the procedure. Potential complications can be detected immediately the immediate haemodynamic changes can be assessed. In addition, the technique is of value in monitoring guiding guidewire and catheter placement for exchange across the atrioventricular valves or within a Mustard procedure. Although the total number of patients who had transoesophageal monitoring during interventional cardiac catheterisation is still limited to date, it may be anticipated that this technique may help to reduce the amount of radiatic contrast agent required. The monitoring of atrial septal defect closure is a further indication for transoesophageal studies in children.¹¹ In fact, the technique appears to be a prerequisite for a high success rate with this new therapeutic approach.

Long term follow up of congenital heart disease

After cardiac surgery via a sternotomy, scar tissue formation often limits transthoracic ultrasound studies. In contrast the transoesophageal approach remains unrestricted. Improved diagnostic insights can be gained in particular lesions or surgical repair involving either venous return to the atrial chambers, or the atrioventricular junction. The advantages of transoesophageal studies in this population include a more detailed assessment of native or prosthetic atrioventricular valve dysfunction or endocarditis.



Transoesophageal visualisation of an overriding and straddling right atrioventricular valve (tricuspid valve) in a 13 kg boy who was previously diagnosed having severe tetralogy of Fallot. (A) Scanning of the inferior portion of the right atrium and the ventricular chambers demonstrates appreciable overriding the tricuspid valve over a rudimentary ventricular septum. The right ventricular cavity is of diminutive size, whereas the left ventricle is enlarged. Chordal attachments of the anterior leaflet of the tricuspid valve are seen to insert into the crest of the ventricular septum (arrow). (B) The inferior leaflet of the tricuspid valve is almost exclusively attached to the left ventricular chamber (arrows). The diagnosis was changed into double inlet left ventricle. The patent chordal attachments of either atrioventricular valve, as documented on transoesophageal imaging, precluded a biventricular repair. A=anterior, IVS=interventricular septum, L=left, LV=left ventricle, P=posterior, R=right, RA=right atrium, RV=right ventricle.

Indications for transoesophageal studies in children

- (1) **Primary diagnosis:**
 - Atrial pathology
 - Anomalous venous connections
 - Atrial septal defects
 - Atrioventricular junction abnormalities
 - Left ventricular outflow obstruction
- (2) **Monitoring:**
 - Perioperative
 - Atrial lesions
 - Atrioventricular valve repair/replacement
 - Mustard/Senning procedure
 - Fontan procedures
 - Continuous monitoring
 - Early postoperative complications
 - Interventional cardiac catheterisation
 - Balloon valvuloplasties
 - Balloon angioplasties
 - Atrial septostomies
 - Venous pathway dilatations
 - Coil embolisations
 - Atrial septal defect occlusion
 - Ventricular septal defect occlusion
- (3) **Follow up:**
 - Venous pathway reconstructions
 - Atrioventricular valve repair/replacement
 - Mustard/Senning procedures
 - Fontan procedures

lesions. After the Mustard or Senning procedure for complete transposition, transoesophageal studies allow a complete evaluation of atrial baffle function,¹² and thus largely influence the need for follow up cardiac catheterisation. After the various modifications of the Fontan procedure, which is used for palliation of a range of complex congenital cardiac lesions, the transoesophageal ultrasound approach provides a most sensitive tool in the definition of residual or acquired haemodynamic lesions and yields new insights into the patterns of the pulmonary circulation.¹³

Limitations

Paediatric transoesophageal echocardiography is a semi-invasive technique that requires either general anaesthesia or heavy sedation. Thus appropriate patient selection is mandatory (table). With the currently available dedicated paediatric scanning equipment studies in children below 4 kg in weight should be performed only if the information likely to be obtained is of importance for appropriate patient management. The present probe technology allows for only single plane imaging of the heart, thus making transoesophageal scanning a strictly tomographic technique. However, it is likely that biplane^{14 15} or multiplane paediatric transoesophageal probes will be designed in the near

future and will further increase the range of diagnostic insights to be obtained.

Conclusion

Transoesophageal echocardiography is a relatively new adjunct to the ultrasound evaluation of congenital cardiac lesions. It is a safe, albeit semi-invasive, technique that rapidly has gained a well defined place in the diagnostic armamentarium of the paediatric cardiologist.

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Jaundice at 14 days of age: exclude biliary atresia

The majority of infants with biliary atresia in the UK are still being referred too late to get optimal benefit from the operation of portoenterostomy. It is now 14 years since we first reported the importance of early referral in this journal.¹ The success of early surgery has been reported repeatedly since then. Over 80% of infants with biliary atresia who underwent surgery before 60 days of age have become jaundice free, compared with 20-35% for those with later surgery.² Results of surgery are less satisfactory in centres operating on few cases.³ It was clear even 14 years ago that infants who cleared their jaundice had a good prospect of long term survival with a good quality of life.¹ This has been confirmed in the last few years from Japan and Europe.⁴ A 15 year survival of 87% has been reported in infants who become jaundice free.⁵ The age at portoentero-

stomy dictates the frequency of survival beyond 10 years of age. For example in one series 17 of 26 (73%) infants operated by 60 days of age survived to 10 years as compared with only eight of 71 (11%) operated after 90 days of age. Thirty of 48 aged from 10 to 33 years have had a completely uncomplicated course while 37 are leading normal lives with no current medical or surgical problems.⁶ Reports from France are similar with the most satisfactory outcome in those operated on by 45 days of age.⁷ Preliminary analysis of patients treated since 1973 at King's College Hospital suggest a similar outcome but few were treated before 45 days.

These observations on the outcome of early surgery are in keeping with what is known of the pathology of biliary atresia.⁸ In the extrahepatic biliary tract there is a pro-

gressive destructive sclerosing inflammatory process. The intrahepatic bile ducts are also involved leading rapidly to a biliary cirrhosis with a mean age of death of 11 months. Excision of the extrahepatic ducts at a stage when there are still patent biliary channels in the porta hepatitis allows the liver to recover sufficiently for normal growth and development even if the liver is fibrotic and the intrahepatic bile ducts are abnormal. Portal hypertension, present in all cases at the time of surgery, can remit but may still cause alimentary bleeding in 10–15%.⁹ Further liver injury may be caused by cholangitis,¹⁰ but this may be less damaging if it occurs more than five years after surgery.¹¹

For the child who does not have a successful portoenterostomy liver transplantation is the other mode of management. The results of liver transplantation are steadily improving with a one year survival rate after one or more transplantation procedures of over 80%.¹² A five year survival of more than 60% has been reported in older children but less than 40% in infants.^{13 14}

Liver transplantation requires many more resources than portoenterostomy. The patient requires lifelong immunosuppression with close supervision for both medical and surgical complication and the longer term prognosis is unknown. Although an important mode of management for end stage liver disease and metabolic disorders, the role of liver transplantation in biliary atresia is secondary to that of portoenterostomy.¹⁵

Despite several publications in this journal, and elsewhere, we find no evidence that infants born with biliary atresia in the UK are being referred earlier. In 1989 the *Lancet* published the findings of a detailed study of the factors that might influence the outcome of surgery and cause delayed referral.² All 50 UK born infants treated for biliary atresia at King's College Hospital in 1985–7 were analysed. Only the age at surgery predicted the outcome. In the three years covered by the study 81%, 54%, and 73% were referred after 6 weeks of age and 46%, 31%, and 35% after 8 weeks of age. All had been jaundiced with persistently yellow urine from the first week of life. One third of families had been reassured repeatedly by midwives, health visitors, or family doctors that the jaundice was physiological. In these instances referral was often initiated at the well baby review at 6 weeks of age. In 60% of cases inappropriate management by hospital paediatric staff contributed to the delay in referral. For example, no investigations to exclude underlying hepatobiliary disease were performed in seven infants with jaundice after 2 weeks of age or in four with jaundice and vitamin K responsive haemorrhagic diathesis. In five instances a diagnosis of breast milk jaundice was made, although this form of jaundice produces an unconjugated hyperbilirubinaemia with no clinical or biochemical evidence of liver disease. In seven instances the clinician was misled by a fall in the serum bilirubin concentration of up to 40 $\mu\text{mol/l}$. A leading article in the *British Medical Journal*¹⁶ and letters in the correspondence columns of both the *British Medical Journal* and the *Lancet* have stressed the measures necessary for the recognition of suspected cases of biliary atresia by 6 weeks of age.

Of 25 infants born in the UK in 1990 whom we have treated for biliary atresia, 63% were referred after 6 weeks of age and 33% after 8 weeks of age, that is, no younger than the age of referral in 1985–7. Although 70% have had a significant drop in their serum bilirubin concentrations after surgery, as yet it is normal in only 50%. We have no reason to suspect that the reasons for delayed referral in the 1990 cohort are in any way different to those in earlier years. At least two were considered to have breast milk jaundice. Parents are angry when they learn that the outcome of surgery may be jeopardised by the time of referral. It is

embarrassing and possibly imprudent in these days of litigation to delve into reasons for delayed referral. The introduction of new techniques^{17 18} and the twice weekly performance of α_1 -antitrypsin phenotyping have excluded genetic, infective, and endocrine disorders more rapidly, reducing the median time between referral and surgery from 14 to eight days. It is difficult to see how the interval can be reduced further if unnecessary laparotomy, with its risks,¹⁹ is to be avoided.

What is required to ensure earlier referral of infants with biliary atresia in the UK?

(1) *The urine of jaundiced infants must be tested for bilirubin and the direct or conjugated bilirubin measured*

The vast majority of infants with biliary atresia are entirely well during the first four to eight weeks of life apart from mild jaundice. The serious nature of the jaundice will be appreciated only if conjugated hyperbilirubinaemia is found. It is always pathological. It must be suspected in any jaundiced infant in whom the urine is yellow as opposed to colourless or clear. All infants with conjugated hyperbilirubinaemia require early identification to minimise the risk of bleeding from vitamin K malabsorption and so that appropriate investigations can immediately be undertaken to identify disorders for which specific medical or surgical treatment is available. It may be the first indication of genetically determined disorders, the identification of which is of considerable importance for the family.²⁰

(2) *The stool must be seen, by the clinician, to determine whether it is yellow or green in colour*

If consecutive stools over a course of two to three days contain no green or yellow pigment biliary atresia is likely. The infant should be referred to a specialised liver centre with the resources to exclude rapidly other causes of complete cholestasis and the surgical expertise to correct biliary atresia effectively. It should be noted that in a minority of patients with biliary atresia the parents give a clear history of the infant passing green or yellow stools before the development of complete cholestasis.

(3) *Systematic screening for hepatobiliary disorders*

Professional education has clearly not succeeded in getting medical staff to perform the two measures that would optimise the management of biliary atresia. Has the time not come to institute systematic screening for hepatobiliary disorders as is done for other relatively rare conditions such as hyperphenylalaninaemia with an instance of approximately 1:4000 live births or congenital hypothyroidism which has a similar incidence?^{21 22} The estimated incidence of biliary atresia ranges from 1:14 000 to 1:21 000 live births.³ The incidence of hepatobiliary disease in early infancy requiring equally early recognition for optimum treatment of infective, metabolic, or endocrine causes is at least five times higher.²³ We would propose that in all infants who remain jaundiced after 14 days of age the urine should be tested for bilirubin and the direct or conjugated bilirubin measured. This could be initiated by the midwife or family doctor. Physiological jaundice almost invariably clears by 14 days of age except in a small proportion of breast fed infants.²⁴ The number of negative tests would be relatively infrequent.

If bile is present in the urine or the conjugated bilirubin is raised the patient should be referred immediately to a paediatrician. If the stools do not contain green or yellow pigment over the course of two to three days the patient

should be referred to a specialist liver centre able to perform portoenterostomy. This change in management could be facilitated with posters emphasising the importance of prolonged jaundice, yellow urine, and the stool colour as early signs of treatable hepatobiliary disease in antenatal, postnatal, and welfare baby clinics or family practitioner centres in which mothers and babies are seen.

(4) Changing the age of well baby review from 6 to 4 weeks of age

Consideration should also be given to changing the age at well baby review from the present 6 weeks to 4 weeks. As well as identifying infants with hepatobiliary disorders it would allow earlier detection of some congenital heart defects, particularly left to right shunts and of subluxation of the hips which may be difficult to detect in the neonatal period. Disturbances in mother-child relationships might be more easily remedied if observed at 4 rather than 6 weeks of age. Since these last two measures have been introduced in Japan the age of infants presenting for surgical correction of biliary atresia has gradually fallen and the outcome has steadily improved.²⁵

Until such measures are instituted in the UK it is essential that paediatricians ensure that the direct bilirubin be measured in all neonates passing through their care, particularly those in whom jaundice is still detectable at 14 days of age. It would not be necessary to screen all well babies, only those who remain jaundiced after 14 days of age. Physiological jaundice almost invariably clears by then except in a small proportion of breast fed infants.²⁴ The urine should be tested for bilirubin and the direct or conjugated bilirubin concentration measured. This could be initiated by the midwife or family doctor.

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ORIGINAL ARTICLES

Does growth hormone treatment improve final height attainment of children with intrauterine growth retardation?

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Abstract

Twenty four children (five girls, 19 boys) who had intrauterine growth retardation were treated with daily subcutaneous biosynthetic human growth hormone, initially in a dose of either 15 or 30 U/m²/week for the first year and in the latter dose for the next two years. Six patients (one girl, five boys) had no dysmorphic signs and 18 (four girls, 14 boys) had signs of Russell-Silver syndrome. All had birth weights below the third centile when adjusted for gestation age and all the children were below the third height centile at the start of treatment. Mean age was 6.3 years (range 2.1-9.7) when growth hormone treatment was started. All had normal growth hormone secretion to either a pharmacological or physiological test.

In the first year of treatment, height velocity SD score increased from -0.75 to +3.6 in the group treated with 30 U/m²/week, and from -0.77 to +1.4 in the lower dose group. After three years of treatment, mean height velocity SD score was +1.1, irrespective of which initial treatment dose had been administered during the first year. There was no difference in the growth response of children with or without dysmorphic features. However, despite the sustained increase in growth rate, there was no significant change in height for bone age SD score, pointing to an unaltered final height outcome.

Growth hormone has been used in the treatment of children with growth hormone deficiency for more than 20 years. Such physiological replacement treatment increases growth velocity and allows the restoration of growth prognosis from the onset of treatment, but in 'standard' dose regimens of between 12 and 15 U/m²/week does not improve final height prognosis beyond the potential at the start of treatment¹; growth hormone treatment allows that potential to be attained. However, since the advent of potentially unlimited supplies of biosynthetic human growth hormone, the pharmacological use of the hormone has been explored in the treatment of short stature which is not due to growth hormone deficiency. The use of growth hormone treatment in short normal children,² Turner's syndrome,³ skeletal dysplasias,⁴ low birthweight syndromes,⁵ and chronic renal failure⁶ has demonstrated that such treatment produces an improvement in short term growth rate. It is only in Turner's syndrome that treatment with growth hormone has shown convincing evidence of improved final height attainment.³ Higher doses of hormone, equivalent to that in naturally

occurring pituitary gigantism, would theoretically lead to an improved final height but there may well be adverse metabolic sequelae.⁷ The pharmacological use of growth hormone in children with short stature has been in the dose range of 15-30 U/m²/week, although 40 U/m²/week has been used in children without changes in glucose tolerance.⁸

Intrauterine growth retardation (IUGR) may be associated with postnatal growth failure and result in a final height in the region of -3.6 SD score.⁹ The pattern of growth in such children continues to be abnormal from intrauterine life through to full maturity. Growth in the first two years of life, which is predominantly dependent on nutrition and growth factors rather than growth hormone, is subnormal.¹⁰ Growth in the middle childhood years, which is predominantly growth hormone dependent,¹⁰ may be due to abnormalities in quantity¹¹ and quality¹² of endogenous growth hormone secretion. The adolescent growth spurt usually occurs early and is reduced in magnitude.⁹

Previous authors have reported an increase in growth velocity in some children with short stature secondary to IUGR but have used growth hormone doses between 30 and 65 U/m²/week.¹³⁻¹⁴ The relatively poor response may have been due to the frequency of administration being only two or three times per week. Using a more optimal frequency of daily administration, a satisfactory growth response has been reported using a lower dose regimen.¹¹⁻¹⁵⁻¹⁶ Eighteen month growth velocity data have been reported in children with IUGR treated with growth hormone¹⁷ but despite a large group of patients, these did not include children with Russell-Silver syndrome.

Previous studies with smaller numbers¹¹⁻¹³⁻¹⁷ have not treated patients for uninterrupted periods of greater than two years. We describe three year data on both growth velocity and growth prognosis in 23 children with short stature and low birth weight, the majority of whom had Russell-Silver syndrome, treated with daily growth hormone. During the first year of this trial, the dose regimen was randomised to either 15 or 30 U/m²/week and has previously been reported⁵ but only in terms of changes in short term growth velocity. We now present three year data on both linear growth and epiphyseal maturation which together point to final height prognosis.

Patients and methods

Twenty four prepubertal patients (five girls, 19 boys) were treated with biosynthetic human

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growth hormone. All had heights below the third centile for chronological age and birth weights less than 2 SD below the mean for gestational age. On clinical examination the children were divided into two groups: those with signs of Russell-Silver syndrome and those without. The criterion used were typical facies, hands and body asymmetry. Minor signs alone, such as clinodactyly of the fifth finger, were considered insufficient evidence of Russell-Silver syndrome. Six patients (one girl, five boys) had no dysmorphic signs and 18 (four girls, 14 boys) were classified as Russell-Silver syndrome. Mean age was 6.3 years (range 2.1–9.7) at the commencement of hormone treatment. All patients had a normal peak serum response (growth hormone concentrations $>10 \mu\text{g/l}$) to either a pharmacological test (response to insulin induced hypoglycaemia or glucagon) or a physiological test (10 hour overnight blood sampling at 15 minute intervals) of growth hormone secretion. It was not the aim of this study to treat children with hormone insufficiency.

All growth hormone was administered by daily subcutaneous injection. The dose was calculated on a surface area basis and updated every six months. During the first year of treatment patients were randomised into two groups: 13 (four girls, nine boys) were treated with $30 \text{ U/m}^2/\text{week}$ and 11 (one girl, 10 boys) were treated with $15 \text{ U/m}^2/\text{week}$. Chronological age and pretreatment growth rate were similar between the two groups. During the second and third years of this trial all patients were treated with growth hormone in a dose of $30 \text{ U/m}^2/\text{week}$.

Growth was assessed by standard anthropometric techniques¹⁸ at intervals of six months and compared with the standards of Tanner *et al.*¹⁹ Bone age was assessed by the methods of Tanner *et al.*²⁰ by one trained observer, performed in a blind fashion. Statistical analysis was by paired *t* test.

Results

In the first year of the trial, mean height velocity SD score increased from -0.75 to $+3.6$ ($p < 0.001$) in the patients treated with $30 \text{ U/m}^2/\text{week}$ (fig 1). By contrast, those treated with the lower dose regimen accelerated from a mean height velocity SD score of -0.77 to $+1.4$ ($p < 0.01$). Because of the improved short term growth velocity using the higher dose regimen, all the patients continued in the second and third years of the study on the higher dose regimen of $30 \text{ U/m}^2/\text{week}$. Growth velocity SD score was sustained at a mean of $+1.1$ after three years, irrespective of which initial treatment group was selected, which was significantly different from pretreatment growth velocity ($p < 0.01$). There was no difference in the response between the sexes or between those with or without Russell-Silver syndrome (fig 1). No adverse effects were experienced and there was no significant change in fasting blood glucose and glycated haemoglobin (HbA_{1c}) concentrations.

The individual growth responses were heterogeneous. One patient (without Russell-Silver syndrome) had no significant improvement of

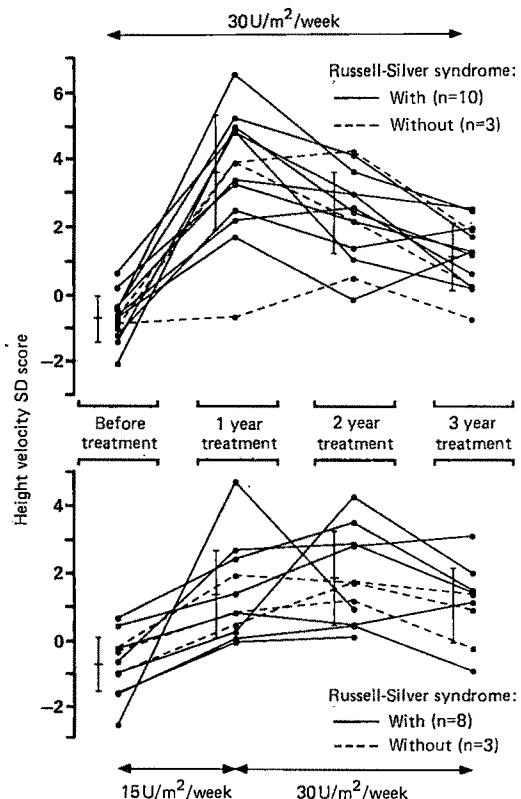


Figure 1 Height velocity SD score in 24 children with short stature secondary to intrauterine growth retardation, both before treatment and during three years of growth hormone treatment. The children were treated with a growth hormone dose regimen of either 15 or $30 \text{ U/m}^2/\text{week}$ during the first year and during the second and third years all children were treated with the higher dose regimen.

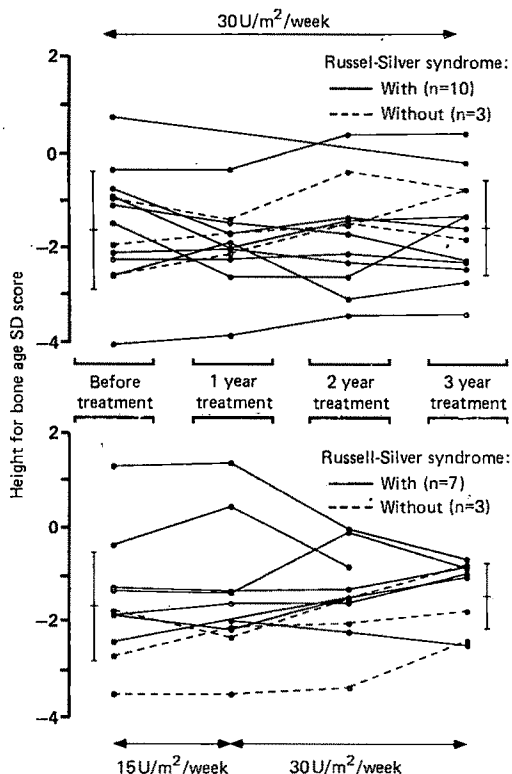


Figure 2 Height for bone age SD score in 24 children with short stature due to intrauterine growth retardation both before treatment and during three years of growth hormone treatment.

growth velocity after nine months of treatment with the lower dose regimen and withdrew from this trial. Mean height of the parents was -3.2

SD score and there was probably an alternative diagnosis in addition to low birth weight to account for this girl's short stature. Two boys with Russell-Silver syndrome, both in the lower dose regimen during the first year, ceased treatment during the third year of the study. One discontinued treatment because the parents were dissatisfied with the response, the other due to non-compliance with the treatment. Only one patient without Russell-Silver syndrome had an inadequate response to growth hormone treatment despite being in the higher dose regimen during the first year: growth velocity SD score was +0.4, and after three years she had a similar value.

Height for bone age score, as a measure of growth prognosis, showed no significant difference ($p > 0.5$) throughout the study from a mean value of -1.6 in both groups at the outset of treatment to -1.5 after three years (fig 2). There was no difference between those children who were treated with the high dose (-1.6) and low dose (-1.4) regimens during the first year of the trial.

Discussion

Children with short stature secondary to IUGR, irrespective of whether dysmorphic signs were present or not, probably represent multiple aetiologies and it is not surprising that there was a heterogeneous growth response to growth hormone treatment. Certainly the children treated with the higher dose regimen grew much faster and it was for this reason that all the children were changed during the second and third years of the study to the higher dose. There was a significant improvement of linear growth response, which continued for at least three years. However, there was no evidence of improved final height, using height for bone age SD score as a measure of height prognosis. The effect of treatment with growth hormone appeared to be an alteration in the 'tempo' of growth without this being translated into improved height prognosis.

Children with IUGR syndromes have an inappropriate advance in epiphyseal maturation which is related to the short adult stature attainment of a mean of -3.6 SD.⁹ It may be that, in a similar way to patients with classical growth hormone deficiency,¹ our patients will attain a final stature which is appropriate for height and bone age to that at the onset of growth hormone treatment. As there was no decrease in height for bone age SD score, which presumably must occur in untreated IUGR children⁹ associated with inappropriate advance of epiphyseal maturation, it may be that our treated patients will have a greater final height than they would otherwise have attained. However, as with any child with a dysmorphic syndrome, the comparison of epiphyseal and metaphyseal morphology, which is fundamental to all methods of bone age determination, may point to a false impression of how much growth potential remains. Only the continuation of clinical trials such as this until final height, will answer the question.

We are uncertain of the effects of growth hormone treatment during puberty in IUGR

children. After three years of our study, all the children remained prepubertal. The growth spurt of puberty is abnormal in children with IUGR⁹; the onset of puberty occurs earlier and there is a lower peak height velocity than in normal children. There is historical²¹ and randomised trial²² data to suggest that growth hormone treatment of children with isolated deficiency of growth hormone results in a reduction in the duration of puberty which is probably dose dependent.²² Moreover, this effect, especially using the high pharmacological doses that we have used, may further compromise pubertal growth. It may be advantageous to delay the onset and duration of puberty using a gonadotrophin releasing hormone analogue²² to permit a longer period for growth in prepuberty and puberty.

There are many other potential indications for the use of growth hormone for short stature when there is no hormone deficiency with the belief that growth hormone treatment will improve final height. Certainly there is considerable evidence to this effect in the treatment of girls with Turner's syndrome³ but convincing evidence is lacking in other patient groups, including IUGR. There may be considerable psychological benefit from improving growth in children with short stature during the middle childhood years^{23, 24} but it is probable, at least in IUGR children, that it is only the 'tempo' of growth that is altered without a corresponding increase in final stature. The initial promise of the therapeutic application of abundant supplies of biosynthetic growth hormone in the treatment of children with short stature may not be realised.²⁵

Gail Hamill was supported by the Child Growth Foundation. We are indebted to Serono (UK) (Ms Ursula Mason, Mr C Eyre, Ms Janis Clayton, and Mr Paul Thomas) for financial, secretarial, and administrative support with this study. We are grateful to Professor A Aynsley-Green and the late Professor M Parkin, Royal Victoria Infirmary, Newcastle upon Tyne, for their help with the treatment of one of the patients in this trial.

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Salbutamol in bronchiolitis

Last year in a report from Toronto it was claimed that nebulised salbutamol (albuterol in the United States) was effective treatment in bronchiolitis.¹ Now workers in Ottawa have produced similar results (Terry PK Lassen and colleagues, *Journal of Pediatrics* 1991;118:807-11).

They performed a randomised, double blind trial comparing nebulised salbutamol with placebo (normal saline). The salbutamol treated patients had a slightly but significantly greater heart rate at 60 minutes after the treatment but there were no significant differences in respiratory rate or oxygen saturation between the two groups at 30 or 60 minutes. The main outcome measure was a clinical score of wheeze and chest retraction (the respiratory distress assessment instrument, RDAI), which gives a score from 0 to 17. The median score before treatment was 8.75 in the treatment group and 8.0 in the placebo group. 30 minutes after treatment the median scores were 6.0 and 7.75 respectively ($p=0.04$).

I have two difficulties with this work. Firstly, the definition of bronchiolitis used in the study includes any wheezing child below the age of 2 years who is not known to have had asthma in the past. Only 58% of the patients had respiratory syncytial virus infection. Secondly, I'm uneasy about the application of statistics in this way to arbitrarily derived clinical scores. The RDAI score is an entirely artificial and contrived parameter. How can it be treated statistically in the same way as a measured continuous variable such as height, oxygen tension, or heart rate? What, too, is the relationship between statistical significance and clinical significance? Shouldn't authors be encouraged to do more to recognise the distinction? On the face of it a difference in change of 2.5 on a 17 point scale doesn't seem all that much, especially as the two observers might differ by up to two points in paired observations. The originators of the RDAI defined clinical improvement as a fall of at least four points in the score and confined their statistical analysis to responders and non-responders on that basis.²

It seems likely to me that many of the children in these North American trials might have been thought by British paediatricians to be suffering from asthma or 'wheezy bronchitis'. I have doubts about the relevance of the results to the management of epidemic bronchiolitis.

ARCHIVIST

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Effect of obesity on endogenous secretion of growth hormone in Turner's syndrome

P W Lu, C T Cowell, M Jimenez, J M Simpson, M Silink

Abstract

Nocturnal growth hormone secretion over a 12 hour period was assessed at 20 minute intervals in 25 prepubertal subjects with Turner's syndrome and 11 normal prepubertal girls of short stature to try and elucidate the relationship between body weight and endogenous secretion of growth hormone in Turner's syndrome. There were no differences in mean growth hormone concentration, age, height, or growth velocity between the two groups. There was an age related decline in mean growth hormone concentration in patient's with Turner's syndrome in contrast to the age related increase in controls. Mean percentage of ideal body weight was significantly higher in the Turner's syndrome group than among controls and it increased with age. There was a strong inverse relationship between mean growth hormone concentration and percentage of ideal body weight in those with Turner's syndrome. Covariate analysis of the multiple linear regression of mean growth hormone concentration on age and percentage of ideal body weight in Turner's syndrome indicated that percentage of ideal body weight had a significant effect on endogenous secretion of growth hormone when age was held constant, but not the other way round.

We conclude that the age related decline in endogenous secretion of growth hormone in Turner's syndrome is partly the result of increasing body weight with age. The significant influences of biological variables such as age and body weight in the interpretation of measurements of endogenous secretion of growth hormone in Turner's syndrome should be emphasised.

Turner's syndrome is the most common sex chromosomal disorder and it is characterised phenotypically by short stature, ovarian dysfunction, and other somatic features. The main sign, which affects almost all children with Turner's syndrome, is short stature. Although its precise pathogenesis is not known, possible contributing factors include intrauterine growth retardation, growth failure during the first decade of life, primary hypogonadism, absent pubertal growth spurt, and skeletal abnormalities.¹⁻⁴ More recently, age related growth hormone deficiency has been reported.⁵⁻⁷

Obesity is one of the somatic features of Turner's syndrome, and the degree of obesity increases with age.^{4 8 9} Impaired endogenous secretion of growth hormone in both total output and pulse frequency, and decreased growth

hormone response to pharmacological stimulation tests, have been observed in simple or idiopathic obese subjects though the mechanism remains unknown.¹⁰⁻¹³ Obesity has not been taken into account in interpreting the decline of endogenous secretion of growth hormone in Turner's syndrome.⁵⁻⁷

The aim of the present study was to examine the relationship of age, obesity, and endogenous secretion of growth hormone in Turner's syndrome.

Subjects and methods

All 25 prepubertal patients with Turner's syndrome (age range 2.0-16.6 years) who were referred to this department between 1986 and 1987 were included in the study. The diagnosis of Turner's syndrome was confirmed by culture of peripheral blood lymphocytes. The karyotype findings were: 45XO (n=13); 46X,i(Xq) (n=6); 45XO/46X,i(Xq) (n=2); 46X,i(Xp) (n=1); and 45XO/46XXr (n=3). Five of the 25 patients had previously had oxandrolone treatment for short stature for periods varying from six months to two years; all medications were stopped at least six months before the study. One patient had primary hypothyroidism and had been receiving thyroxine replacement for 18 months. All subjects were clinically and biochemically euthyroid at the time of sampling of growth hormone.

All 11 prepubertal girls (age range 4.1-13.1 years) with familial or constitutional short stature who were referred to this department for assessment of short stature during the same period (1986 and 1987) were included in the control group. All subjects were healthy, free from systemic disease, and had no evidence of endocrine abnormality. No subject had received growth promoting treatment before the study. Consent was obtained for the investigation.

PROTOCOL

All subjects were followed up at quarterly intervals for at least one year before the overnight growth hormone sampling. Auxological data were recorded at each visit. Height was measured with a Harpenden stadiometer. Weight was measured on a scale with an accuracy of 0.1 kg. Each subject was admitted to the metabolic ward in the afternoon. No fasting or special diet was required. Patients received a normal dinner at 5.30 pm before which a 22G catheter was inserted into a forearm vein. Blood samples for measurement of growth hormone concentration

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were taken at 20 minutes intervals from 8.00 pm to 8.00 am the next morning. A total of 37 samples were collected. Plasma was immediately separated and stored at -20°C until assayed.

The growth hormone response to pharmacological stimulation was assessed after overnight sampling. Thirty two patients had an arginine stimulation test combined with an insulin hypoglycaemia stimulation test, and four patients had a clonidine stimulation test, after overnight fasting. Arginine 0.5 g/kg body weight (maximum 30 g) was given by intravenous infusion as a 10% solution in normal saline. Blood samples were collected at -15, 0, 30, 45, and 75 minutes. Short acting insulin (Actrapid, Novo) of 0.1 unit/kg body weight was then given intravenously; all patients achieved biochemical hypoglycaemia with serum glucose concentrations of <2.2 mmol/l. Blood samples were taken at 0, 15, 30, 45, 60, 75, 90, and 120 minutes. Clonidine 0.125 mg/ m^2 was given orally; blood samples were taken every 30 minutes for 150 minutes.

Plasma was also taken for assessment of thyroid and renal function, and estimation of luteinising hormone, follicle stimulating hormone, oestradiol, and insulin-like growth factor I (IGF-1) concentrations. Bone age was assessed at the date of study and estimated by Greulich and Pyle's method.¹⁴

ASSAYS

Growth hormone concentrations were measured by a radioimmunoassay (RIA) that was done by a double antibody technique with a sensitive and specific antiserum. The first antibody was a rabbit growth hormone antibody used at a final dilution of 1/1 000 000. Each specimen was assayed in duplicate, and the mean value expressed in $\mu\text{g/l}$.¹⁵ All samples from one subject were measured in the same assay. The coefficients of variation between assays were 21.5% at the level of 2 $\mu\text{g/l}$; 8.5% at 8.5 $\mu\text{g/l}$, and 6.9% at 17.5 $\mu\text{g/l}$. The intra-assay coefficients were 10.6%, 5.3%, and 6.6%, respectively. The average minimum detectable concentration calculated from 40 assays was 0.14 $\mu\text{g/l}$ (range 0.02–0.3).

Gonadotrophins and oestradiol were measured in duplicate with commercial immunoassay kits as follows: follicle stimulating hormone (Delfia hFSH kit; Pharmacia) with interassay coefficient of variation of 8.3% at 23.1 IU/l and 10.4% at 4.2 IU/l; luteinising hormone (Delfia hLH kit; Pharmacia), interassay coefficient of variation of 8.0% at 14.0 IU/l and 7.1% at 4.5 IU/l; oestradiol (¹²⁵I-Estradiol Direct Radioimmunoassay Kit; Baxter Dade AG), with an interassay coefficient of variation of 8% at 252 pmol/l. The minimal detectable concentration of oestradiol was 18.5 pmol/l.

IGF-1 was measured by RIA¹⁶; the inter-assay coefficients of variation were 13.8% at 6.3 nmol/l, 8.7% at 36.3 nmol/l, and 14.3% at 171.6 nmol/l. The intra-assay coefficients of variation were 13.3% at 6.0 nmol/l, 11.8% at 31.8 nmol/l, and 14.6% at 207.6 nmol/l.

ANALYSIS OF OVERNIGHT GROWTH HORMONE PROFILES

Overnight growth hormone profiles were analysed using the PULSAR algorithm modified for growth hormone.¹⁷ The original PULSAR algorithm was designed particularly for the analysis of gonadotrophins,¹⁸ but (unlike gonadotrophins) the interpeak concentrations of growth hormone are usually undetectable with current assays.¹⁹ The modified PULSAR algorithm sets a smooth but variable baseline with a maximum of 1 $\mu\text{g/l}$. Peaks are defined as a subset of values of duration n above this baseline, all the points of which are at least G units of the SD of the RIA assay in magnitude. As n increases G decreases, so the program selects narrow high peaks and broad peaks that may be lower. The $G(n)$ values used were the default figures given by Merriam and Wachter in the original PULSAR algorithm: $G(1)$ 3.98, $G(2)$ 2.40, $G(3)$ 1.68, $G(4)$ 1.24, and $G(5)$ 0.93. The following variables were computed: overall mean growth hormone concentration of 37 samples from the 12 hour measurement, peak amplitude, and the number of pulses.

AUXOLOGICAL DATA

Height SD scores, weight SD scores, and percentage of ideal body weight were derived according to National Center for Health Statistics growth standards.²⁰ Birth weight SD scores were calculated according to gestation from the Australian data of Kitchen *et al.*²¹ Growth velocity was calculated over 12 months. Growth velocity SD scores for bone age were derived using the clinical longitudinal standards for height and height velocity for American children by Tanner and Davies.²²

STATISTICAL ANALYSIS

SAS (System for Elementary Statistical Analysis) software was used to analyse the data.²³ Results are shown as mean (95% confidence intervals (CI)) unless otherwise stated. Data for all variables except weight SD scores, percentage of ideal body weight, and luteinising hormone and follicle stimulated hormone concentrations were normally distributed, so group means were compared by Student's t test and differences between means given with 95% CI in parentheses; associations were assessed with linear regression and correlation; multiple linear regression was used to examine interrelationships between variables after controlling for covariates, and to test whether the slopes of the linear regressions were the same in both groups by testing for statistical interaction. For skewed distributions we used Wilcoxon's rank sum test to compare the two groups, and medians are given; associations were examined by Spearman rank correlations. Fisher's exact test was used to compare proportions in the two groups. All significance tests are two sided and probabilities of less than 0.05 were accepted as significant.

Results

The girls with Turner's syndrome were older

than the controls though there were no significant differences in chronological age, bone age, age for height, height SD score, growth velocity SD score, or birth weight SD score between those with Turner's syndrome and controls (table 1). Bone age was delayed in both groups, but there was no significant difference in the degree of delay (table 1). There were no significant differences in any of the variables between the 13 girls with karyotype 45XO and the other 12 subjects who had either mosaicism or abnormal X chromosome.

The weight SD score was significantly higher in those with Turner's syndrome than controls ($p=0.003$) (table 1). The difference in percentage of ideal body weight between those with Turner's syndrome and controls was also highly significant ($p=0.0001$) (table 1). Fourteen girls with Turner's syndrome had percentage of ideal body weight greater than 120% and were defined as obese,²⁴ but none of the subjects in the control group had a percentage of ideal body weight of more than 120%. Obese subjects were older than non-obese subjects ($p=0.002$, table 2). There were, however, no significant differences in height SD score, bone age, and mean delay between chronological age and bone age between obese and non-obese patients (table 2).

There was no significant difference in plasma oestradiol concentrations between those with Turner's syndrome (mean: 52.8 pmol/l, 95% CI: 43.1 to 64.5 pmol/l) and controls (mean 46.4 pmol/l, 95% CI: 32.4 to 60.5 pmol/l). Plasma oestradiol concentrations did not correlate with

measurements of endogenous growth hormone output in either group. Plasma gonadotrophins concentrations were significantly higher in those with Turner's syndrome than in controls (follicle stimulating hormone: mean 32.1, 95% CI 22.0 to 42.3 IU/l compared with mean 1.3, 95% CI 0.6 to 2.1 IU/l, $p=0.001$; luteinising hormone: mean 7.1, 95% CI 4.5 to 9.6 IU/l compared with mean 0.3, 95% CI 0.1 to 0.5 IU/l, $p=0.0001$).

GROWTH HORMONE SECRETION

There were no significant differences between patients with Turner's syndrome and controls for any of the variables computed from overnight growth hormone profiles (table 3), and none of the variables correlated significantly with height SD score or growth velocity SD score in either group.

In two of the 11 controls (18%) and nine of the 25 with Turner's syndrome (36%) the peak amplitude of their nocturnal growth hormone profiles was suboptimal ($<10 \mu\text{g/l}$), but not significantly so ($p=0.44$). Nine of the 25 subjects with Turner's syndrome (36%) had suboptimal peak growth hormone responses to pharmacological stimulation ($<10 \mu\text{g/l}$) but none of the control subjects showed an abnormal response ($p=0.03$). Four children with Turner's syndrome had suboptimal growth hormone responses in both endogenous growth hormone profile and pharmacological stimulation tests.

There was no significant correlation between

Table 1 Clinical data of 25 patients with Turner's syndrome and 11 control subjects with familial or constitutional short stature

	Patients with Turner's syndrome (n=25)		Control subjects (n=11)	
	Mean	95% CI	Mean	95% CI
Chronological age (years)	10.2	8.9 to 11.4	8.5	6.5 to 10.5
Bone age (years)	9.1	8.0 to 10.1	7.1	5.5 to 8.7
Mean delay between chronological age and bone age (years)	1.7	1.1 to 2.3	1.8	1.3 to 2.3
Height SD score	-3.3	-3.6 to -2.9	-3.5	-3.8 to -3.1
Birth weight SD score according to gestational age	-1.4	-1.9 to -1.0	-0.8	-1.5 to 0.07
Growth velocity SD score according to bone age	-3.4	-4.6 to -2.3	-2.9	-3.6 to -2.3
Weight SD score	-1.2	-1.7 to -0.8*	-2.2	-2.7 to -1.7*
Percentage of ideal body weight	127.8	117.7 to 137.9**	100.4	93.5 to 107.2**

* $p=0.003$; ** $p=0.0001$.

Table 2 Comparison of obese and non-obese patients with Turner's syndrome

	Obese (n=14)		Non-obese (n=11)		p Value
	Mean	95% CI	Mean	95% CI	
Age (years)	11.8	10.7 to 12.9	8.1	6.2 to 10.0	0.002
Bone age (years)	9.8	9.0 to 10.7	7.9	6.1 to 9.7	0.09
Mean delay between chronological age and bone age (years)	2.2	1.5 to 2.9	1.0	0.2 to 1.8	0.06
Height SD score	-3.3	-2.8 to -3.7	-3.3	-2.7 to -3.8	0.92
Mean growth hormone concentration ($\mu\text{g/l}$)	1.7	1.2 to 2.2	2.7	2.1 to 3.4	0.02
No of pulses	3.5	2.8 to 4.2	5.2	3.9 to 6.4	0.02
Peak amplitude ($\mu\text{g/l}$)	11.5	7.7 to 15.4	16.8	12.2 to 21.4	0.10

Table 3 Mean overnight growth hormone profiles in 25 patients with Turner's syndrome and 11 control subjects with familial or constitutional short stature

	Patients with Turner's syndrome (n=25)		Control subjects (n=11)	
	Mean	95% CI	Mean	95% CI
Mean growth hormone concentration ($\mu\text{g/l}$)	2.1	1.7 to 2.6	2.3	1.8 to 2.9
Peak amplitude ($\mu\text{g/l}$)	13.9	10.8 to 16.9	12.6	9.5 to 15.7
No of pulses	4.2	3.5 to 5.0	4.4	3.4 to 5.3

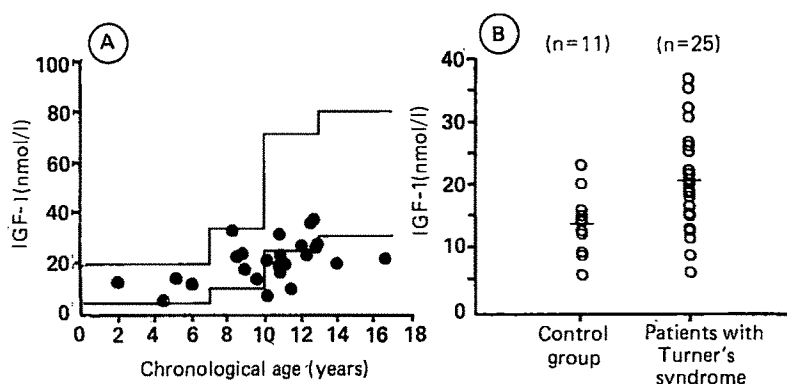


Figure 1 Plasma insulin-like growth factor (IGF-1) concentrations in subjects with Turner's syndrome and reference range plotted against age (A), showing an age related increase in IGF-1 in patients with Turner's syndrome ($r=0.46$, $p=0.01$). (B) Mean plasma IGF-1 concentration (horizontal bar) is significantly higher in patients with Turner's syndrome than controls ($p=0.03$).

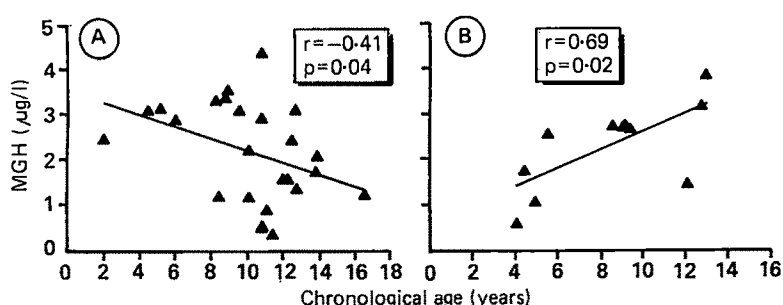


Figure 2 Mean growth hormone (MGH) concentrations plotted against age for girls with Turner's syndrome (A) and control subjects (B). There is an age related decline in patients with Turner's syndrome and an age related increase in controls.

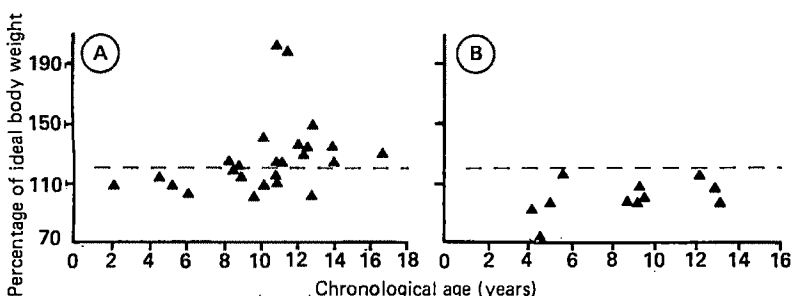


Figure 3 Percentage of ideal body weight plotted against chronological age for girls with Turner's syndrome (A) and control subjects (B). Age related obesity occurs in Turner's syndrome ($r=0.57$, $p=0.003$) but not in controls. Fourteen patients in the Turner's syndrome group had percentage ideal body weight greater than 120% (horizontal dotted line) and were defined as obese.

the peak growth hormone response from pharmacological stimulation tests and any of the measurements made from overnight growth hormone profiles in either group. The peak growth hormone concentration after the pharmacological stimulation test did not correlate with any of the auxological variables (including body weight) or with age.

IGF-1

IGF-1 concentrations increased with age in patients with Turner's syndrome ($r=0.46$, $p=0.01$) (fig 1A) but not in controls, though a comparison of the linear regression between the two groups was not significant (p for difference between slopes $=0.08$). IGF-1 was significantly higher in those with Turner's syndrome than in controls (mean 19.8 , 95% CI 16.4 to 23.2 nmol/l compared with mean 13.7 , 95% CI 10.7 to 16.6

nmol/l; $p=0.03$) (fig 1B). Because girls with Turner's syndrome were slightly older, we examined the relationship between IGF-1 concentration and age by taking age difference into account; after controlling for the difference in age between the two groups, the IGF-1 concentration was 4.7 nmol/l (95% CI: -0.6 to 10.0 nmol/l) higher in those with Turner's syndrome than in controls ($p=0.09$). Eleven of the 25 patients with Turner's syndrome (44%) and four of the controls (36%) had IGF-1 concentrations lower than the laboratory's reference range ($<2SD$ scores for age). IGF-1 concentrations had no association with either auxological data or measurements of endogenous growth hormone profiles.

EFFECT OF AGE

There was a highly significant difference in the relationship between mean growth hormone concentration and age for those with Turner's syndrome and controls (p for difference between slopes $=0.005$). In those with Turner's syndrome there was a significant age related decline in mean growth hormone concentration ($r=-0.41$, $p=0.04$) (fig 2) and peak amplitude ($r=-0.50$, $p=0.01$); in contrast, there was an age related increase in the control group (fig 2).

EFFECT OF OBESITY

There was a highly significant age related increase in percentage of ideal body weight in patients with Turner's syndrome ($r=0.57$, $p=0.003$) (fig 3A). Two of the girls with Turner's syndrome had extremely high values, which tend to skew the distribution and exaggerate the relationship with age. If these two points are omitted, percentage of ideal body weight increases by 2.2% (95% CI 0.7 to 3.7%) with each year of age ($p=0.01$); after adjusting for age, percentage of ideal body weight was 18.0% higher in Turner's syndrome (95% CI 9.2 to 26.9) than in controls ($p=0.0002$). There was no significant correlation between age and percentage of ideal body weight in controls (fig 3B).

There was also a significant weight related decline in endogenous secretion of growth hormone in those with Turner's syndrome (fig 4), and this relationship was not altered when the two extremely obese girls were omitted from the analysis ($r=-0.52$, $p=0.02$). In Turner's syndrome this decline was observed in all measurements of overnight growth hormone profiles: mean growth hormone concentration ($r=-0.62$, $p=0.0009$) (fig 4A), peak amplitude ($r=-0.54$, $p=0.0006$), and the number of pulses ($r=-0.52$, $p=0.008$). The relationship between percentage of ideal body weight and endogenous secretion of growth hormone in Turner's syndrome is further illustrated in figure 5. There was no significant association between mean growth hormone concentration and percentage of ideal body weight in controls (fig 4B).

The difference in overnight growth hormone profiles between obese ($n=14$) and non-obese ($n=11$) patients with Turner's syndrome was significant. Obese subjects had fewer pulses and

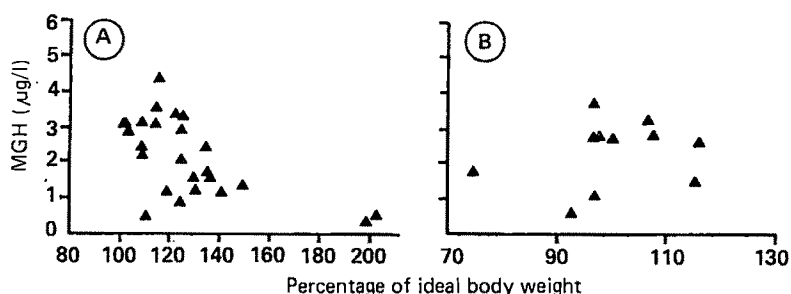


Figure 4 Percentage of ideal body weight plotted against mean growth hormone (MGH). In Turner's syndrome (A) MGH concentration decreases as percentage of ideal body weight increases ($r = -0.62$, $p = 0.0009$) but there is no association between body weight and age in controls (B). Horizontal scale in fig 4(B) is different from that in fig 4(A).

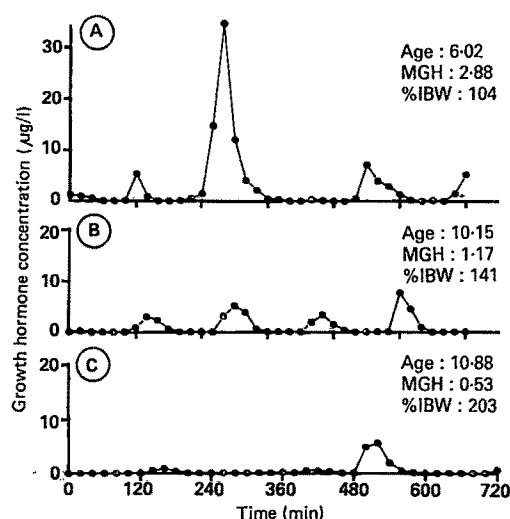


Figure 5 12 Hour nocturnal growth hormone profiles for three patients of different ages with Turner's syndrome. As percentage ideal body weight (%IBW) increased mean growth hormone (MGH) secretion and the growth hormone pulse amplitude decreased.

lower mean growth hormone concentrations than non-obese patients (table 2).

COVARIATE ANALYSIS

Because both age and body weight had significant effects on endogenous secretion of growth hormone, the inter-relationships among these three variables in Turner's syndrome were further explored by multiple linear regression of mean growth hormone concentration on age and percentage of ideal body weight. The effect of percentage of ideal body weight on mean growth hormone concentration remained significant after controlling for age ($p = 0.005$), but age had no significant effect on mean growth hormone concentration after adjusting for percentage of ideal body weight.

Discussion

This study confirms that there is an age related decline in endogenous secretion of growth hormone in prepubertal subjects with Turner's syndrome. This decline contrasts with the increase in endogenous secretion of growth hormone in the prepubertal subjects who were controlled for the same sex, were of similar age, and had similar height and growth velocity SD

scores. Massarano *et al* reported this finding, though their study lacked controls.⁵ The aetiology of this decline in endogenous secretion of growth hormone is unknown.

Primary hypogonadism in Turner's syndrome may have a crucial role. Endogenous oestradiol is thought to be important in the pulsatile amplification of endogenous secretion of growth hormone in normal adults.²⁵ Physiological doses of oestradiol enhance the endogenous secretion of growth hormone in castrated and intact female baboons.²⁶ Suppression of ovarian function in girls with central precocious puberty results in decreased endogenous secretion of growth hormone.²⁷ Conflicting results have been reported in girls with Turner's syndrome who were treated with physiological doses of oestrogen, whereas enhancement of endogenous secretion of growth hormone was noted in one study,²⁸ no change was found in another.⁵ In the present study we found no difference in the plasma oestradiol concentration between prepubertal subjects with Turner's syndrome and prepubertal normal controls of short stature, and no correlation between plasma oestradiol concentrations and measures of endogenous growth hormone in patients with Turner's syndrome. The possibility that oestradiol may have a role in the decline of endogenous growth hormone had not, however, been totally excluded as primary hypogonadism was evident in patients with Turner's syndrome from the raised gonadotrophin concentrations.

Obesity is difficult to define but easy to recognise; it is defined here as more than 120% of ideal weight for height.²⁴ Normal weight standards in children, however, remain difficult to determine. There are several methods of estimating fatness in childhood. Estimation of body composition from anthropometric measurements are both practicable and useful. We prefer percentage ideal body weight rather than body mass index (weight/height²), as percentage ideal body weight not only takes height into account, but also provides easily recognised results. More than half the patients with Turner's syndrome in this study were obese, compared with none of the subjects in the control group. As the subjects were selected by their presentation to an endocrine clinic because of short stature not because of their body weight, this finding could be interpreted as indicating that there was a high incidence of obesity in prepubertal subjects with Turner's syndrome. Obesity in Turner's syndrome is age related, as indicated in this and several previous studies.^{4 8 9} As with simple obesity,^{12 13} there is a strong inverse relationship between body weight and a number of measures of growth hormone in nocturnal growth hormone profiles (mean growth hormone concentration, peak amplitude, and pulse frequency). Covariate analysis indicated that the decline in endogenous secretion of growth hormone in Turner's syndrome was strongly related to obesity but not to age. We believe therefore that obesity could partly explain the decline of growth hormone secretion in patients with Turner's syndrome.

The possibility that obesity is causally related

to the decrease in endogenous growth hormone must be considered. Growth hormone stimulates lipolysis,²⁹ which explains the decrease in subcutaneous fat in growth hormone deficient children being treated with growth hormone supplement.³⁰ Adult subjects with growth hormone deficiency tend to be obese with decreased muscle mass,³¹ but no clear association has been made between growth hormone deficiency and obesity in childhood. Obesity was not mentioned in original descriptions of growth hormone deficiency, although children with hypopituitarism tend to have more fat in some regions of the body.³² Furthermore, the response of growth hormone to pharmacological stimuli is enhanced in obese subjects with no clinical evidence of growth hormone deficiency if they lose weight.^{11 33} We believe, therefore, that obesity is a cause rather than a consequence of growth hormone deficiency in the girls with Turner's syndrome.

The total amount of growth hormone secreted is related to the pulse amplitude and frequency. The change in growth hormone secretion with age, stature, and pubertal stage is said to be a function of the pulse amplitude but not of its frequency.³⁴ In contrast, the decline in secretion of growth hormone in simple obesity¹³ and in the present study in Turner's syndrome was associated with decreased pulse frequency as well as amplitude. This association between body weight and diminishing pulse frequency in obese subjects suggests an abnormality in the hypothalamic control of growth hormone secretion through growth hormone releasing hormone and somatostatin.³⁵ Speculation on the mechanism of this decrease in growth hormone pulse frequency has focused on the negative feedback of high plasma IGF-1 or high free fatty acid concentrations, or both.^{36 37} Our data do not confirm the hypothesis about IGF-1 concentrations because although they were higher in patients with Turner's syndrome than in controls, they were at the lower end of the reference range for the prepubertal age group. An alternative explanation for the decreased pulse frequency is that the sensitivity of the growth hormone assay does not allow us to detect low amplitude pulses occurring at normal frequency.¹⁹

Prepubertal children with simple obesity are usually tall for their age,³⁸ and have advanced bone age.³⁹ Our findings in obese prepubertal subjects with Turner's syndrome, however, contrast with findings in subjects with simple obesity as there was no difference in height SD scores, bone age, or growth velocity between obese and non-obese groups.

It may be postulated that there is a connection between growth hormone secretion status and short stature in Turner's syndrome because of the concomitance of decline in endogenous growth hormone secretion and severe growth retardation in prepubertal girls with Turner's syndrome. We could not find any association between measures of growth hormone secretion and growth, and this supports the observations made by Massarano *et al.*⁵ Furthermore, the fact that subjects with Turner's syndrome require a higher dose of exogenous growth hor-

mone than subjects with growth hormone deficiency to achieve the same growth velocity suggests the possibility of partial end organ resistance to growth hormone in Turner's syndrome, rather than clinical growth hormone deficiency.⁴⁰

The plasma concentration of IGF-1 depends on age, growth hormone, and nutrition.⁴¹⁻⁴⁵ A normal growth hormone-IGF-1 axis has been suggested in patients with Turner's syndrome,⁴⁶ but in the present study, the plasma concentrations of IGF-1 in those with Turner's syndrome were not totally dependent on growth hormone concentrations. Subjects with Turner's syndrome had age related increases in IGF-1 despite the age related decline in growth hormone concentrations. This discrepancy has been commented on in Turner's syndrome⁵ and in simple obesity.^{44 47} Although we found no direct relationship between IGF-1 and percentage of ideal body weight, it is apparent that obesity must be considered as a regulating factor of circulating IGF-1 concentrations. The possibility that the interrelationship between growth hormone secretion, IGF-1, and nutrition is mediated by the nutritional regulation of the growth hormone receptor is currently being investigated.⁴⁸

In conclusion, our study has confirmed the existence of an age related decline in secretion of growth hormone and increasing obesity in prepubertal children with Turner's syndrome. This decline in endogenous secretion of growth hormone can be attributed to the increased body weight in girls with Turner's syndrome. We emphasise that the interpretation of endogenous growth hormone secretion requires critical assessment of biological variables including age, puberty, and weight.

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Autosomal recessive hypoparathyroidism with renal insufficiency and developmental delay

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Abstract

Four children (two boys and two girls) with hypoparathyroidism, renal insufficiency, and developmental delay are described. They were the products of consanguineous marriages in three related Asian families presenting over a six year period. All the children died within the first 15 months of life despite treatment. Postmortem examination on one child showed absent parathyroid glands. We believe these children represent a previously undescribed syndrome that appears to be inherited in an autosomal recessive manner.

Early onset idiopathic hypoparathyroidism is rare. It is usually a sporadic condition but familial forms have also been reported. It may occur in isolation or associated with other abnormalities. We report four children from three related families who presented in infancy with hypocalcaemia due to hypoparathyroidism. They also had evidence of renal insufficiency, failure to thrive, and developmental delay. This combination has not previously been described and appears to be inherited in an autosomal recessive manner.

Case reports

CASE 1

This boy was born in 1982 weighing 2100 g at 36 weeks' gestation (VI.1 in figure). He was the first child of Asian parents who were first cousins. He became lethargic on the ninth day of life and investigations showed evidence of a metabolic acidosis (pH 7.18, base excess -17 mmol/l), with hypocalcaemia (1.32 mmol/l), and hyponatraemia (115 mmol/l). He was treated with sodium bicarbonate, calcium gluconate, and the vitamin D analogue alfacalcidol. Further investigations gave normal results and included an infection screen, plasma 17 hydroxyprogesterone, serum amino acid and ammonia, and urinary organic acid concentrations. He had evidence of a distal renal tubular acidosis because he was unable to achieve a urinary pH below 5.5. Over the next few months he continued to have evidence of hypocalcaemia and failed to thrive. He was reassessed at the age of 5 months. At this time his weight was 3.4 kg (2.5 kg less than the third centile), height 61 cm, and head circumference 39 cm (both less than the third centile). He was generally hypotonic with poor head control. Investigations (see table) confirmed hypocalcaemia and hyperphosphataemia with a normal magnesium (0.93 mmol/l).

He had normal values for plasma albumin and alkaline phosphatase. He had evidence of renal insufficiency and a compensated metabolic acidosis. His calculated index of phosphate reabsorption (tubular maximum reabsorption of phosphate/glomerular filtration rate, $TmPO_4/GFR$)¹ was 3.6 mmol/l (normal range 1.15-2.26 mmol/l). Plain abdominal x ray films showed no evidence of renal calcification, and a renal ultrasound demonstrated a bright cortex and prominent pyramids. A renal biopsy specimen showed normal glomeruli and birefringent crystals in the tubules which appeared to be oxalate. He had raised values for oxalate: creatinine ratio at 105:1 (quoted normal less than 70:1) and a presumptive diagnosis of primary hyperoxaluria was made. He was initially discharged on alfacalcidol and pyridoxine but was readmitted one month later because of vomiting and weight loss. His metabolic abnormalities were unchanged and he subsequently died.

CASE 2

This girl was born in 1985 weighing 3400 g at term. She was born to Asian parents who were first cousins and she was a cousin to case 1 (VI.7 in figure). She was admitted at the age of 3 months because of poor feeding dating from birth and failure to thrive. Her weight, length, and head circumference were all below the third centile and she was generally hypotonic and developmentally delayed. Investigations (see table) showed a metabolic acidosis, hypocalcaemia, hyperphosphataemia, and renal insufficiency. There was evidence of a distal renal tubular acidosis because she was unable to lower the urinary pH below 6 when the bicarbonate was 13 mmol/l. She had normal values for plasma albumin and alkaline phosphatase. Her tubular maximum reabsorption of phosphate ($TmPO_4/GFR$) was 3.44 mmol/l (normal

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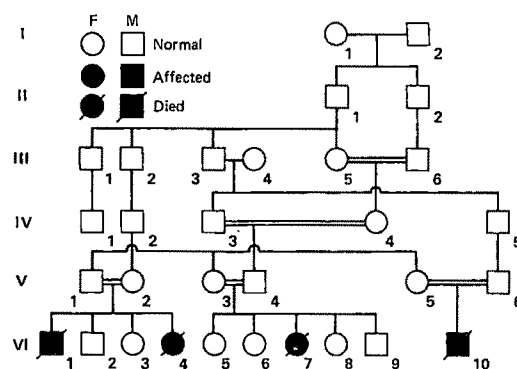
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Family tree of affected children.

Biochemical abnormalities at presentation

Case No	Bicarbonate (mmol/l)	Calcium (mmol/l)	Phosphate (mmol/l)	Urea (mmol/l)	Creatinine (μ mol/l)	Potassium (mmol/l)
1	12.6	1.6	4.5	18.9	109	6.7
2	17.0	1.49	2.66	10.7	*	6.4
3	11.0	1.21	2.36	10.1	*	7.7
4	8.0	1.71	2.61	12.0	100	9.3

*Not done at presentation.

range 1.15–2.6 mmol/l).¹ She had a raised 24 hour urine oxalate excretion of 0.48 mmol/1.73 m²/day (normal range <0.46 mmol/1.73 m²/day).² A renal biopsy specimen showed mainly fetal type glomeruli with a prominent microcystic appearance and dilatation of the proximal tubules. A few oxalate crystals were seen in the tubules. She was initially treated for primary hyperoxaluria and commenced on pyridoxine. Subsequent results of her urinary oxalate excretion confirmed a raised oxalate:creatinine ratio of 159 mmol:mmol (normal range 14–25 mmol:mmol) but no increased excretion of glycolate or glycerate as would be expected in primary hyperoxaluria. She was readmitted at 11 months with deteriorating renal function (concentrations of urea 23.9 mmol/l and creatinine 187 μ mol/l). Her weight was less than 5 kg and she had profound developmental delay with very poor head control. After discussion with the parents it was decided she be offered palliative treatment only. She subsequently died a few weeks later.

CASE 3

This girl was born in 1988 weighing 1590 g at 35 weeks' gestation. She was a sibling of case 1 (VI.4 in figure). She made reasonable progress in the first week of life, but at 8 days developed a metabolic acidosis (see table) with renal insufficiency and hypocalcaemia. She was treated with sodium bicarbonate, calcium gluconate, and alfacalcidol. She subsequently had frequent convulsions over the next seven weeks. Because of the previous family history suggestive of primary hyperoxaluria, a liver biopsy was performed at 5 weeks of age. The biopsy specimen did not demonstrate any features of oxalosis and no evidence of deficiency of the specific enzyme hepatic alanine glyoxylate aminotransferase.³ She continued to have hypocalcaemia, convulsions, and poor weight gain and at the age of 3 months was transferred to another hospital for further investigation. At that time her weight was only 2.85 kg with head circumference and length also being well below the third centile. She had profound hypotonia and showed no obvious response to visual or auditory stimuli. The following problems were revealed on further investigation:

(1) *Hypoparathyroidism*—An initial parathyroid hormone concentration measured in the original hospital at age 24 days using an intact molecule assay (IncStar) gave a normal result of 88 pg/ml (normal range 20–80 pg/ml). However, a C-terminal assay gave a result of <250 pg/ml (normal range 250–600 pg/ml). A concentration measured in the second hospital at the age of 3 months using an intact molecule assay (Allegro)

gave a result of 4 ng/l (normal range 11–35 ng/l). This was when her calcium was only 1.21 mmol/l and therefore is very low for the degree of hypocalcaemia. Her tubular maximum reabsorption of phosphate (TmPO₄/GFR) was 3.36 mmol/l (normal range 1.48–3.3 mmol/l).¹ Further investigations into the aetiology of the hypoparathyroidism showed no evidence of parathyroid antibodies, normal immunoglobulins, low normal T lymphocyte numbers, but normal in vitro responses. She was treated with large doses of alfacalcidol and a dose of 0.75 μ g per day was found necessary to maintain her serum calcium in the normal range.

(2) *Renal insufficiency*—The serum creatinine concentration remained fairly static between 100–120 μ mol/l with a serum urea of 10–15 mmol/l. The hyperkalaemia settled from an initial potassium concentration of 6.9 to 4.3 mmol/l. There was evidence of a distal renal tubular acidosis requiring bicarbonate supplements. However, the acidosis resolved with correction of the hypocalcaemia. A renal ultrasound showed normal sized but echogenic kidneys. A renal biopsy was not performed because of her poor condition.

(3) *Convulsions and developmental delay*—She had numerous convulsions in the first few weeks of life which did not always respond to intravenous calcium. They were eventually controlled with a combination of clonazepam and sodium valproate. A computed tomogram showed mild generalised cerebral shrinkage and several small foci of low density parenchyma in the left hemisphere that had the appearance of infarcts. A urine metabolic screen for amino acids, organic acids, and mucopolysaccharides gave normal results. Visual evoked responses revealed intact visual pathways. Brain stem auditory evoked responses showed an absent response on the right. She remained severely developmentally delayed and hypotonic and did not achieve any developmental milestones.

(4) *Failure to thrive*—Despite an energy intake of at least 0.84 MJ/kg/day she showed negligible weight gain. There was no improvement on a diet free of cows' milk or an elemental peptide diet. Investigations showed excess split fats on stool microscopy, no reducing substances in her stool, and normal faecal chymotrypsins. Insufficient sweat was obtained for a sweat test. Chromosomes and thyroid function tests were normal. A barium meal showed appreciable oesophageal reflux, which showed no improvement with thickened feeds or the use of domperidone or cisapride. She remained in hospital and died at the age of 7 months. As in cases 1 and 2 parental consent was not obtained for a postmortem examination.

CASE 4

This boy was born in 1988 weighing 2800 g at term. He was born to Asian parents who were second cousins and he was a cousin to the other three cases (VI.10 in figure). At birth other than bilateral talipes equinovarus he was well. He was admitted at the age of 3 weeks with a history of poor feeding, irritability, vomiting, and poor weight gain. He was 5% dehydrated, wasted, and hypotonic. He had a profound metabolic acidosis (see table) hyperkalaemia, hypocalcaemia, renal insufficiency, and hyperphosphataemia. He was rehydrated and commenced on bicarbonate and calcium supplements. A parathyroid hormone concentration at the age of 3 weeks using an intact molecule assay (IncStar) was normal at 95 pg/ml (normal range 20–80 pg/ml) but a value of less than 250 pg/ml was obtained using a C-terminal assay (normal range 250–600 pg/ml). This was at a time when his serum calcium was only 1.4 mmol/l. He had evidence of excess faecal fat excretion of 56% (normal less than 25%) and a normal sweat test. Despite correction of his hypocalcaemia with a dose of alfacalcidol of 0.75 µg/day he continued to have feeding difficulty with failure to thrive. At the age of 4 months he was 1.3 kg less than the third centile and he was developmentally delayed by at least two months. He was subsequently investigated at the Hospital for Sick Children in London. The following abnormalities were shown:

(1) *Hypoparathyroidism*—An intact parathyroid hormone measurement (IncStar) gave a concentration of <16 ng/l (quoted normal range 20–80 ng/l). A subsequent concentration using the intact molecule assay (Allegro) was low (8 ng/l) at the age of 9 months. His immune status was also investigated revealing normal immunoglobulins, low T cell numbers, but normal in vitro lymphocyte responses.

(2) *Renal insufficiency*—He had a raised creatinine concentration of 99 µmol/l. A renal ultrasound showed increased echogenicity of the renal cortex. Micturating cystogram showed no evidence of reflux and a technetium labelled dimercaptosuccinic acid scan no evidence of scarring. A renal biopsy was not performed.

(3) *Developmental delay*—He had generalised hypotonia with a persistent asymmetric tonic neck reflex. He had hypertonic legs with hyperreflexia. He had a persistent grasp reflex and showed signs of scissoring when held upright. He was unable to sit and had no parachute reflexes at the age of 7 months. An electroencephalogram was normal for his age. Visual evoked responses were normal. Brain stem auditory responses showed no responses bilaterally. A computed tomogram showed a single focus of dense calcification in the right corona radiata and minimal generalised cerebral atrophy.

(4) *Failure to thrive*—His weight was 5.4 kg at age 7 months. Length and head circumference were between the third and tenth centiles. Other investigations performed and found to be normal were plasma amino and organic acids, barium swallow, chromosomes, and thyroid function tests.

Despite being maintained on alfacalcidol,

sodium bicarbonate, and calcium supplements his condition continued to deteriorate and he subsequently died at the age of 14 months. Permission for a postmortem examination was obtained and showed the following features. Detailed histological sections through the neck failed to detect any parathyroid glands but a normal thymus gland. There was evidence of nephrocalcinosis and microcalcification in the brain with ischaemic necrosis of the hippocampal gyri. No other anatomical or developmental malformations were found.

Discussion

The four children presented in a very similar manner and had the following features in common: hypoparathyroidism, renal insufficiency with a renal tubular acidosis, failure to thrive, and developmental delay. In addition, cases 3 and 4 had evidence of nerve deafness. Although parathyroid hormone concentrations were not obtained in cases 1 and 2, the hyperphosphataemia, hypocalcaemia, and values for tubular maximum reabsorption of phosphate are consistent with hypoparathyroidism. The presentation of these four children in three related Asian families is consistent with autosomal recessive inheritance.

Three main forms of persistent idiopathic hypoparathyroidism have been described in children. Familial isolated hypoparathyroidism which may present in the neonatal period is an isolated defect with no other abnormalities. In addition to sporadic occurrence sex linked recessive⁴ and autosomal dominant⁵ forms have been reported. The second form of hypoparathyroidism recognised is that which occurs in association with developmental abnormalities of the third and fourth pharyngeal pouches (DiGeorge's syndrome). These individuals have congenital heart defects, usually of the aortic arch, impaired cell mediated immunity, and may have characteristic dysmorphic features. Inheritance is usually sporadic, but autosomal dominant and recessive inheritance has been reported. The third form of hypoparathyroidism seen in children is felt to be autoimmune in nature. Other autoimmune disorders occur in association, notably Addison's disease, but also alopecia areata, hypothyroidism, ovarian failure, and diabetes. Chronic mucocutaneous candidiasis is usually present. Circulating antibodies to parathyroid glands and other endocrine tissues may be detected. Steatorrhoea has also been reported as a feature in this form.⁶

The children described in this paper do not readily fit into any of these three categories. They certainly do not have an isolated hypoparathyroidism and they also lack features consistent with a partial or complete DiGeorge's syndrome. Although there was no evidence of other autoimmune disorders, it is reported that features of these may not occur for several years after the onset of hypoparathyroidism.⁷ Parathyroid autoantibodies were not found in case 3, but these may only be present in 38% of cases.⁷ There was also some evidence of steatorrhoea in cases 3 and 4, so it is possible they belong to the autoimmune group. The absence

of parathyroid gland tissue seen at postmortem examination in case 4 may be due to one of two mechanisms. It may represent atrophy of the parathyroid glands as has been reported in autoimmune hypoparathyroidism or may be due to agenesis of parathyroid tissue due to a defect in embryogenesis.

Familial hypoparathyroidism has also been reported in association with some diverse developmental abnormalities. Dahlberg *et al* reported two brothers who also had lymphoedema, pulmonary lymphangiectasia, renal insufficiency, and prolapsing mitral valves.⁸ Barakat *et al* reported two brothers who had hypoparathyroidism, nerve deafness, and steroid resistant nephrotic syndrome.⁹ A renal biopsy specimen taken from one of the boys revealed fetal like glomeruli. There are some similarities between these children and those reported here in that two of the children in our series had documented nerve deafness and fetal like glomeruli was seen at biopsy in case 2. However, none of our cases had hypoalbuminaemia or a level of proteinuria consistent with nephrotic syndrome.

There are some similarities between our cases and those recently described by Richardson and Kirk¹⁰ and Sanjad *et al*.¹¹ Richardson and Kirk described four children with failure to thrive, dysmorphic features, developmental delay, and hypoparathyroidism. They all had medullary stenosis of the long bones on skeletal survey. They were the products of consanguineous marriages of Middle Eastern parents. Sanjad *et al* described 12 children from Saudi Arabia, 10 of whom were products of consanguineous marriages. They all had hypoparathyroidism, severe growth failure, psychomotor retardation, and dysmorphic features similar to those described by Richardson and Kirk. Our cases differ in that all had renal insufficiency as a prominent feature, had no obvious dysmorphic features, and no abnormalities on skeletal survey. In addition two of our cases had absent auditory evoked responses whereas hearing was normal in the patients described by Richardson and Kirk. Although there are many similarities, we believe our cases represent a separate unique syndrome. It is likely that the genetic basis for these conditions will be similar.

Several features of the cases merit further discussion. The presence of apparently normal values for parathyroid hormone (using an intact molecule assay) in the first month of life in cases 3 and 4 is unusual. However, there are very few data available on parathyroid hormone concentrations in the newborn and it may well be that the assay was also measuring parathyroid hormone related peptide thus giving the

erroneous impression that parathyroid function was normal. It appears clear that the developmental delay seen in these children was not a consequence of untreated hypoparathyroidism as case 4 was commenced on treatment early, but still had developmental delay despite normocalcaemia. Finally, the first two cases reported illustrate the diagnostic difficulty that can occur as a result of the finding of oxalate crystals on renal biopsy and raised urinary oxalate excretion. It appears clear in retrospect that these children had secondary hyperoxaluria possibly as a consequence of malabsorption. It is important that raised concentrations of the oxalate metabolites or absence of the specific enzyme hepatic alanine glyoxalate aminotransferase⁴ are demonstrated before a diagnosis of primary hyperoxaluria is made. The existence of reliable parathyroid hormone assays in recent years that are specific for the intact molecule also aided the investigation of these children. Inheritance of this disorder would appear to be autosomal recessive in nature and currently attempts are being made to isolate the gene defect in this extended family which may provide a means of antenatal diagnosis.

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Bone marrow transplantation in sickle cell anaemia

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Abstract

Sickle cell anaemia is still responsible for severe crippling and death in young patients living in developing countries. Apart from prophylaxis and treatment of infections, no active treatment can be safely proposed in such areas of the world. Therefore a bone marrow transplantation was performed in 12 patients staying in Belgium and planning to return to Africa.

Twelve patients, aged between 11 months and 23 years (median 4 years), underwent a HLA identical bone marrow transplantation. The conditioning regimen included oral busulphan for four consecutive days (4 mg/kg) followed by four days of intravenous cyclophosphamide (50 mg/kg). In 10 patients the engraftment was rapid and sustained. A further patient suffered transient red cell hypoplasia and another underwent a second bone marrow transplantation from the same donor at day 62 because of graft rejection. All patients are alive and well with a follow up ranging from 9-51 months (median 27 months). In all cases a complete cessation of vaso-occlusive episodes and haemolysis was observed as was a change in the haemoglobin pattern in accordance with the donor's electrophoretic pattern.

Sickle cell anaemia remains a disorder with a high morbidity and mortality rate. The mortality rate in Zaire is not known but is likely to be similar or even worse than that in Jamaica¹ where 10 to 20% of children with sickle cell anaemia die during the first decade of life from severe infections, acute splenic sequestration, or cerebrovascular accidents. In the USA a prospective study gives a mortality rate of 3-3% before the age of 20 years.² Apart from prophylaxis of infections with oral penicillin and vaccination against *Streptococcus pneumoniae*, the treatment is mainly symptomatic: analgesics and transfusions. New therapeutic approaches include stimulation of fetal haemoglobin production,³ but also manipulation of the oxygen saturation curve of haemoglobin S,⁴ reduction of the mean corpuscular haemoglobin concentration by increase of the water content of sickle cells,^{5,6} and modification of the membrane adhesive properties of the sickle cell.⁷ Further studies and controlled trials are necessary to evaluate the benefits and side effects of these treatments. Another approach, which unfortunately cannot be offered to all patients but has the advantage of reversing the clinical and haematological manifestations of the disease, is bone marrow

transplantation. Preliminary results were reported in 1988 and encouraged us to pursue this approach.⁸

Methods

This study was approved by the ethical committee of our hospital. All risks of the treatment procedures were explained to the patients, donors, and relatives and informed consent was obtained.

PATIENT SELECTION

Twelve black patients with sickle cell anaemia underwent a HLA identical bone marrow transplantation. Eleven were from Zaire and one from Cameroon. Three were in Belgium for three to four years because their parents were studying. One patient aged 23 years was a student at our university. The eight other patients came to Belgium for the procedure and all 12 planned to return as soon as possible to their native country. Patients were selected because of the severity of the disease, their young age (11 months-23 years, median 4 years), a good general condition, the absence of HIV infection, and the presence of a healthy HLA identical donor in the family. The severity of the disease was difficult to evaluate. All patients had a median of four (range 1-6) vaso-occlusive episodes per year and occasionally required blood transfusions (table). The youngest patient (patient 2) was 11 months at the time of transplantation and had suffered only one vaso-occlusive episode but had already been transfused twice. The oldest patient (patient 10) was 23 years old at the time of transplantation and was ready to accept any treatment, even potentially dangerous, instead of suffering four to five vaso-occlusive episodes per year. She had an arthrodesis of the right hip at the age of 14, a left hip prosthesis at the age of 16, and severe limitation of movement of the left shoulder, all problems being sequelae of infection or aseptic necrosis. The other patients had no chronic organ damage at the time of bone marrow transplantation. Details of the patients are shown in the table.

Haemoglobin components were separated and quantified by fast protein liquid chromatography.⁹ The haemolysates were chromatographed through a strong cation exchange column (Mono S^RHR 5/5) for determination of haemoglobins A, S, and F and detection of haemoglobin A₂ was done using an anion exchange column (Mono Q^RHR 5/5). In some patients the β : α chain ratio was measured in order to look for α thalassaemia association.¹⁰

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Details of patients who had bone marrow transplantation

Patient No	Sex	Age (years)	Mean No of vaso-occlusive episodes/year	Mean No of transfusions/year	Haemoglobin pattern			Haemoglobin (g/l)	Mean corpuscular volume (fl)	Mean corpuscular haemoglobin (g/l)
					S (%)	F (%)	A ₂ (%)			
1	F	3	4	3	79.1	20.3	0.6	76	79.8	324
2	M	0.9	1	2	77.3	22.0	0.7	64	72.6	332
3	F	4	4	3	78.4	20.0	1.6	76	83.7	321
4	F	9	4	0-1	90.2	9.0	0.8	85	86.9	366
5	F	3	4	0-1	89.5	9.4	1.1	76	76.0	323
6	M	7	6	0-1	88.2	9.3	2.5	73	93.0	321
7	F	1	5	0-1	90.2	7.5	2.3	76	77.5	337
8	M	13	4	0-1	93.4	3.1	3.5	74	71.0	373
9	F	7	4	0-1	90.7	6.1	3.2	96	84.0	330
10	F	23	5	0-1	94.5	1.4	4.1*	84	77.0	307
11	F	1.7	2	2	74.6	22.5	2.9†	71	79.0	337
12	F	12	3	2	92.4	3.9	3.7	76	72.0	354

* β : α =1.6, † β : α =1.2.

DONORS

Donors were identical for HLA-A, B, C, and D/DR locus as determined by serological typing and mixed lymphocyte culture. When possible, genotypical analysis of the entire family was performed. Donors were siblings in 11 cases and the father in one (patient 4), their age ranged from 1-32 years. They either had a normal haemoglobin electrophoresis pattern (AA, n=4) or were carriers of the sickle cell trait (AS, n=8). When possible the haemoglobin electrophoresis of the entire family was also studied. In all cases it was shown that the parents were carriers of the sickle cell trait.

SUPPORTIVE CARE

Prophylaxis of infections included oral colistin, vancomycin, and amphotericin B during the inpatient period, oral acyclovir (10-20 mg/kg) for one year, and intravenous hyperimmune plasma containing cytomegalovirus antibodies twice a week for three months and once a week for two months. In patients who received short term steroid treatment for acute graft-versus-host disease (GVHD), co-trimoxazole (3 mg trimethoprim/kg) was given during one year for *Pneumocystis carinii* prophylaxis.

CONDITIONING REGIMEN AND GVHD PROPHYLAXIS

Busulphan (4 mg/kg/day) was given orally for four consecutive days followed by four days of intravenous cyclophosphamide (50 mg/kg/day). In patients above 12 years of age preparation included also a thoracoabdominal irradiation (750 cGy over six hours) with an 18 MeV linear accelerator, the lungs being shielded.

Prevention of GVHD included intravenous cyclosporin (5 mg/kg/day) for 14 to 21 days and then oral cyclosporin (12 mg/kg/day) for six to 12 months, serum concentrations were kept between 100 and 150 ng/ml (measured by radioimmunoassay). In patients older than 12 years intravenous methotrexate (10 mg/m²) was given on days 1, 3, 6, and 11 after transplantation.

Patients who developed acute GVHD received methylprednisolone (2 mg/kg/day) until a complete response was obtained, and the dosage was then tapered over several days.

In patient 4, a second bone marrow trans-

plantation was performed on day 62 because of graft rejection. The conditioning regimen was as described by Storb *et al.*¹¹ Chemotherapy included four days of intravenous cyclophosphamide (50 mg/kg/day), and a 10 hour infusion of antithymocyte globulin (Upjohn, 30 mg/kg/day) 12 hours after the first, second, and third doses of cyclophosphamide. The day before transplantation the patient underwent thoracoabdominal irradiation (750 cGy over six hours) with an 18 MeV linear accelerator (lungs being shielded). Bone marrow was infused 36 hours after the last dose of cyclophosphamide. GVHD prophylaxis included cyclosporin and methotrexate as described above.

Results

SHORT TERM FOLLOW UP

In 10 patients the bone marrow engrafted without major complications. Patient 4 rejected the graft after the engraftment had been confirmed; a second transplant was performed on day 62 with an uneventful recovery. Patient 8 had prompt white cell and platelet recovery but the red cell series engraftment remained poor until five months after transplantation. Patients 1, 4, 6, and 8 had grade I-II acute GVHD of short duration. Bone marrow transplantation related toxicity was analysed according to the World Health Organisation (WHO) recommendations.¹² It included oral mucositis (WHO score 3) and diarrhoea (WHO score 1) in 11 patients. In patient 10 mucositis was severe (WHO score 4) and renal function impaired (WHO score 2) until day 21. One patient developed a *Klebsiella pneumoniae* bacteraemia that responded promptly to an aminoglycoside- β lactam combination. The same antibiotic regimen was successfully used in all the other patients who developed a fever of unknown origin while neutropenic. The time necessary to recover a neutrophil count above $1 \times 10^9/l$ and a platelet count above $150 \times 10^9/l$ was 14-30 days (median 19 days) and 17-110 days (median 39 days) respectively.

LONG TERM FOLLOW UP

The follow up ranges from 9-51 months (median 27 months). All 12 patients are in good general condition and none has had a vaso-occlusive

episode since transplantation. Patient 8 required blood transfusions during the first five months but is now doing well with a follow up of 22 months. In 11 patients the chromatographic pattern of the haemoglobin became similar to that of the donor (AA, $n=3$; AS, $n=8$). Although the donor was AA in patient 3 a small amount of haemoglobin S is still present (3%) 36 months after transplantation, suggesting mixed chimerism. In the six patients having a donor of the opposite sex, cytogenetic studies confirmed the presence of bone marrow cells from the donor. Twelve months after bone marrow transplantation patient 1 developed autoimmune thrombocytopenia as shown by an increase in the number of megakaryocytes on bone marrow examination and by a fourfold increase in antiplatelet antibodies. Thrombocytopenia was first thought to be a sign of chronic GVHD, although there was no other symptom, and cyclosporin was restarted without success. Intravenous gammaglobulins were given without response. An increase in the platelet count was transiently noticed after steroids and azathioprine. Isotopic studies performed 18 months after transplantation showed increased splenic destruction of platelets and a platelet half life of 2.5 days (normal 4 ± 0.5 days). Splenectomy was performed 24 months after transplantation, but the response was only transient and the treatment with steroids was resumed in addition to azathioprine first, cyclophosphamide afterwards, and ascorbic acid. Finally, 40 months after transplantation and independently of all previous treatments, the platelet count became normal and the medications could be progressively stopped.

Among the 12 patients, seven went back to their native country and continue to do well.

Discussion

The first reported bone marrow transplant performed in a child with sickle cell anaemia was for acute myeloblastic leukaemia.¹³ Conversion of sickle cell anaemia into sickle cell trait suggested that bone marrow transplantation might be another possible treatment. To decide whether transplantation should or should not be offered to patients with sickle cell anaemia morbidity and mortality have to be compared between transplanted patients and patients receiving another treatment.

Our series is the first one to report on 12 young patients probably cured by bone marrow transplantation. One patient rejected the graft but was successfully regrafted from the same donor. Mixed lymphocyte culture was negative, there was no infection, no blood products from the donor had been transfused, and cytotoxic antibodies were absent. A possible reason for rejection is that, although recipient and donor were phenotypically identical, they were not genotypically identical, the donor being the father. Another patient required blood transfusions during the first five months because of prolonged erythroblastopenia. This patient's blood group was O Rh positive and the donor's was A Rh positive. Delayed red cell series engraftment can occur with ABO incompatible

bone marrow transplantation.¹⁴ Full engraftment is usual several months after transplantation as was the case in our patient. In our 12 patients acute phase toxicity was acceptable and reversible in all of them. As far as long term toxicity is concerned, one patient developed immune thrombocytopenia one year after transplantation but complete remission was observed two years later. Risks related to the procedure can probably best be compared with those encountered in thalassaemic patients, the conditioning regimen being similar. In thalassaemic patients the incidence of chronic GVHD is 10%.¹⁵ Although our series is small, chronic GVHD and rejection might be less often encountered because patients with sickle cell anaemia did not have complications of transfusion treatment. They had no hepatomegaly and concentrations of ferritin were only slightly raised. The young age of the patients is another factor for a good prognosis as far as chronic GVHD is concerned.¹⁶ Cytomegalovirus related complications were not seen.

The follow up is too short to evaluate the influence of bone marrow transplantation on growth, fertility, and secondary tumours. Growth and fertility will be difficult to evaluate because most children with sickle cell anaemia experience delayed puberty and are almost invariably thin. Concerning fertility, men with sickle cell anaemia have low sperm counts and women have normal fertility but with a high incidence of miscarriages and stillbirths.¹⁷ Toxicity of the conditioning regimen (busulphan and cyclophosphamide) is currently being evaluated in patients with acute non-lymphocyte leukaemia and chronic myeloid leukaemia.¹⁶

On the other hand, with conventional treatments morbidity and mortality rates in sickle cell anaemia remain high with at least 10 to 20% of children dying during the first decade of life.¹ The majority of patients cannot afford long term antibiotic treatment for prophylaxis of infections, and blood transfusions should be avoided whenever possible in countries with a high incidence of HIV infection.¹⁸ Modern therapeutic approaches are based upon the knowledge that fetal haemoglobin interferes with sickling by reducing the tendency for polymerisation.¹⁹ Therefore, attempts have been made to stimulate the synthesis of fetal haemoglobin by azacytidine and hydroxyurea. Hydroxyurea seems more promising but patients have to be monitored very carefully because effectiveness is achieved at concentrations likely to cause bone marrow depression.³ Hopes were raised that erythropoietin might have an additive effect while decreasing toxicity of hydroxyurea,²⁰ but a recent report showed that erythropoietin was of no benefit.²¹ Other studies are in progress with agents causing a better oxygenation of the red cell,¹⁴ reducing the mean corpuscular haemoglobin concentration,^{5,6} or modifying membrane properties of sickle cells.⁷ These approaches need however to be further studied and controlled trials are necessary.

At the present time bone marrow transplantation is the only treatment offering the possibility of eliminating the sickling phenomenon and its consequences. Benefits and risks related to the procedure must be balanced. Patients should be

old enough to have an understanding of the severity of their disease but young enough to be in good general condition, free of HIV infection, without chronic organ damage, without haemochromatosis, and at a low risk of developing chronic GVHD. Furthermore, bone marrow transplantation should essentially be proposed to patients wishing to return to their native countries where patients with sickle cell anaemia are at risk of malnutrition and infections.

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Respiratory rate: measurement of variability over time and accuracy at different counting periods

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Abstract

The respiratory rates/minute of 97 children were monitored every 10-15 minutes over one hour, by an observer and by pneumogram, at which times two 30 second and one 60 second counts were obtained. The children were under 5 years of age with lower respiratory tract infections (n=20), upper respiratory tract infections (n=34), or controls without acute respiratory infection (n=43). The difference between respiratory rate count determined simultaneously by observation and pneumogram in relation to their mean count was analysed for the 60 second counting period, 30 plus 30 second period, and the 30 second period doubled. The mean difference for the 60 second period was 1.79, for the 30 plus 30 second period 1.42, and for the 30 second period doubled 1.72. The variability between respiratory rate counts determined by observation and pneumogram was significantly lower in counts obtained when the subject was sleeping and higher when agitated compared with obtaining a count when the subject was awake and calm or feeding. The variability was also significantly lower in subjects with lower respiratory tract infections compared with those with upper respiratory tract infections and control subjects without respiratory symptoms. In the same patient, over the one hour, 50% of the 60 second counts varied by up to 14 breaths/minute and 75% by up to 21 breaths/minute. The least variability was seen in children with a lower respiratory tract infection, who tended to maintain their rapid breathing in contrast to those with an upper respiratory tract infection and controls without respiratory symptoms. About 10% of initial 30 second counts, 12% of 60 second, and 16% of initial and repeat 30 second attempts to obtain accurate counts failed. Failures occurred more frequently in children <2 months of age and those agitated. The data from this study suggest that one minute's counting either at a stretch or in two blocks of 30 second intervals is better than counting the respiratory rate for 30 seconds, when the child is either awake and calm or when asleep.

infection include a respiratory rate of 60 or greater in infants under 2 months of age, 50 or greater in infants age 2 to 11 months, and 40 or greater in children 12 months and older. The presence of indrawing in a child without wheezing is an indication of severe disease requiring hospitalisation. The accuracy of diagnosis relies on the ability to obtain an accurate respiratory rate/minute and to recognise the presence or absence of lower chest wall indrawing. As this latter sign is fairly constant from patient to patient and its recognition can be taught easily (E A F Simoes, E McGrath, unpublished observation), obtaining an accurate respiratory rate count is the most important variable in the programme. As the respiratory rate depends on a single count, the natural variability in the rate may affect the classification of disease.

This study was undertaken to determine the optimal time period for counting the respiratory rate in children under 5 years of age and to determine factors that affect its variability over time. It has been suggested that a 30 second count, doubled, be used to obtain a respiratory rate.² Because of the natural variability of the respiratory rate and the presence of periodic breathing in infants <6 months of age,³ a 60 second count has been recommended by the WHO.¹ One study that used three, 15 second counts with a stethoscope to obtain a respiratory rate, documented baseline rates over 50 breaths/minute during the first six months of life.⁴ It is possible that counting for a longer period of time might result in more failed attempts because of movement of the child, or other distractions. Hence the specific aims of this study were:

- (1) To determine the accuracy of respiratory rate counting by comparing observer counts with those obtained from an electronic pneumogram for 30 second and 60 second counting intervals.
- (2) To determine the effect of (i) the age, (ii) the illness, and (iii) the state of the child (that is, whether the child was sleeping, calm and awake, feeding, or agitated) on the accuracy of counting.
- (3) To determine the natural variability in the respiratory rate over one hour.
- (4) To determine how many attempts at obtaining a respiratory rate resulted in failures and identify the reasons for failures.

Subjects and methods

Subjects were prospectively enrolled in the study and consisted of children less than 5 years of age seen at three locations within the

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The World Health Organisation (WHO) Case Management Program for Acute Respiratory Infections uses respiratory rate thresholds and the presence of lower chest wall indrawing to decide if a patient has pneumonia and needs hospitalisation or outpatient antibiotics.¹ Criteria for diagnosis of a lower respiratory

teaching hospital of the University of Colorado Health Sciences Center (UCHSC), including the paediatric outpatient department, the general paediatric inpatient ward, and the normal newborn nursery.

Eligibility criteria included parental consent, age less than 5 years, and illness (if present) of less than two weeks' duration. Exclusion criteria included presence of any chronic illness, the child having an illness which would likely involve dehydration, children who were inconsolably agitated, and presence of a current illness of greater than two weeks' duration. Subjects were enrolled on a first come basis without consideration given to sex or race. Parents of subjects were asked to read and sign a UCHSC Institutional Review Board approved consent form giving their permission for their child's participation in the study.

A medical history focusing on the child's current illness (if any) and a medical history (focusing particularly on any previous respiratory conditions) was then obtained. A physical examination was then performed that carefully assessed respiratory findings.

After enrolment into the study, standard paediatric silver/silver chloride electrodes were placed on the subject's mid-axillae at the costal margins and leads from an Aequitron 2916 respiratory/heart rate monitor were attached. The monitor was linked to a General Scanning RS2-5P strip chart recorder which produced real time traces of chest wall excursions on Aequitron 8285-12 1 mm graduated strip paper.

The monitor and trace were switched on once the child had become quiet after any disturbance produced by application of the electrodes. A strip chart running rate of 1 mm/second was used during periods when the observer was not counting the respiratory rate. Synchronous with the human observer beginning his respiratory rate count, the strip chart running rate was switched to 5 mm/second. This produced a trace pattern that very clearly delineated the beginning and end of the observer counting interval and allowed accurate counting on the strip. When movement artefact altered baseline recording, peaks and troughs of the respiratory excursion usually remained discernible. However, when movement artefact prevented accurate interpretation, the pneumogram was considered non-evaluable.

The observer counted the respiratory rate for 30 seconds, waited for a period of approximately one minute and repeated the above procedure counting instead for 60 seconds. After waiting again for one minute, another count of 30 seconds was made. The respiratory rate and state of the child (awake and calm, feeding, sleeping, and agitated), were recorded on a flow sheet. Mild agitation was defined as motion non-disruptive to counting; severe agitation disrupted counting and was considered a reason for failure. In addition, during each counting interval the observer recorded any counting attempts that failed and the reason for the failure (that is, crying, coughing, yawning, apnoea, deep sighs, severe agitation, feeding movements, and distraction or losing track of the time by the observer).

After obtaining this set of 30 second/60 second/30 second counts, the observer waited for 12-15 minutes before repeating the set of counts described above. These sets of counts were obtained five times for each subject evaluated. The counts on the strip chart were read by a blinded observer at the end of the study after all patients were enrolled.

The respiratory rate measurements are presented as the mean difference between the respiratory rate determined by observation and pneumogram and the SD of the difference. The agreement between the respiratory rate counts obtained by observation was compared with those obtained from an electronic pneumogram using the graphical technique of Bland and Altman.⁵ In addition, the resulting variances (SD^2) of the difference between rates from the two methods were compared between time intervals as well as between age groups, diagnoses, and child states with Bartlett's test for homogeneity of variance. Where a significant difference was found, pairwise comparisons, by means of an F test for equality of variance, were carried out and reported.

The data for the counting failures are reported as the percentage of failures out of the total observations. These percentages were compared using the normal approximation to the test for equality of binomial proportions.

Results

PATIENT POPULATION

There were 97 patients studied, approximately equally distributed over the three age groups: less than 2 months ($n=27$), 2-11 months ($n=37$), and 12-48 months ($n=33$). The median age of children studied was 6 months and the mean age 10 months. Fifty one of these children were boys. Of the 97 children studied, 20 had lower respiratory tract infections, 34 upper respiratory tract infections, and 43 were controls who did not have any respiratory symptoms.

Of the 34 patients categorised as having an upper respiratory tract infection, 26 had uncomplicated viral upper respiratory infections, four had pharyngitis, three croup, and one influenza. For the purpose of the study, the three patients with croup were classified as having an upper respiratory infection. Of the 20 children with lower respiratory tract infections, 12 had bronchiolitis, four interstitial pneumonia (probably viral in aetiology), two a lobar pneumonia, one an aspiration pneumonia, and one pneumonia with effusion. Nineteen of these 20 patients had abnormal chest radiographs. In one child, a radiograph was not obtained.

RESPIRATORY RATES ACCORDING TO METHOD AND THE DURATION OF THE COUNTING PERIOD

The numbers, ranges, and means (SD) of the respiratory rates determined simultaneously by observation and pneumogram are presented in table 1 for the initial 30 second, the 60 second, and repeat 30 second counts. The pneumogram tracing was non-evaluable in 12 of 1382 paired respiratory rate counts.

Table 1 Respiratory rates according to method and duration of counting period

Method	Period	No of counts	Minimum	Maximum	Mean (SD)
Pneumogram	Initial 30 second	458	10.0	43.0	22.6 (6.3)
Observed	Initial 30 second	462	7.0	42.0	21.8 (6.5)
Pneumogram	60 second	459	19.0	90.0	44.0 (12.3)
Observed	60 second	463	20.0	85.0	42.2 (11.7)
Pneumogram	Repeat 30 second	453	10.0	50.0	22.4 (6.4)
Observed	Repeat 30 second	457	9.0	52.0	21.5 (6.5)

Table 2 Mean difference between 60 second observed and pneumogram respiratory rate counts by age, child state, and diagnosis

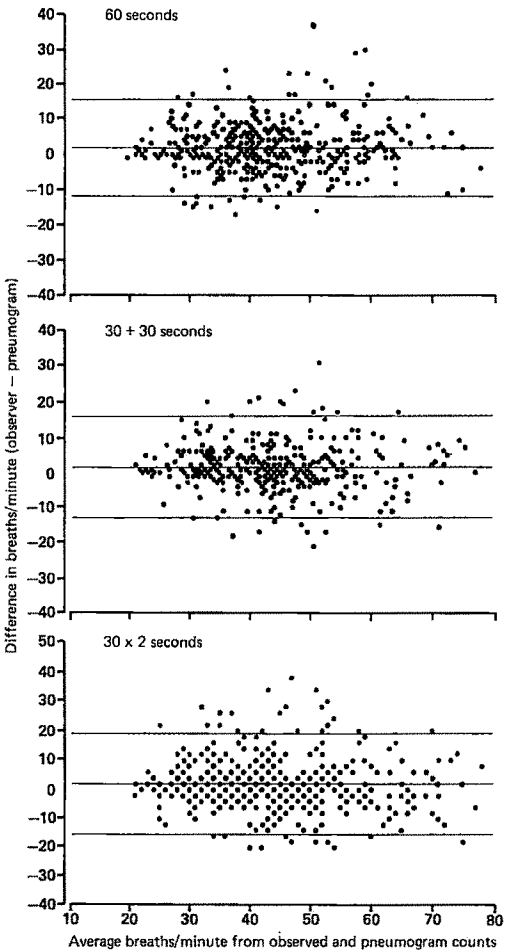
Characteristic	Paired observations	Range		Mean (SD)
		Minimum	Maximum	
Age (months):				
<2	134	-17	23	1.5 (6.4) (1)
2-11	173	-16	37	1.9 (7.6)
≥12	148	-15	23	1.9 (6.3) (1)
Child state:				
Calm/awake	162	-15	37	2.1 (7.2)
Feeding	44	-16	21	2.3 (6.9)
Sleeping	142	-15	17	1.3 (4.7) (2)
Agitated	107	-17	30	1.6 (8.5) (3)
Diagnosis:				
Lower respiratory tract infection	96	-11	20	0.8 (5.3)
Upper respiratory tract infection	157	-15	37	2.0 (7.3) (4)
Control	202	-17	30	2.0 (7.1) (4)

Results of tests for equal variance: (1) $p<0.01$; variance significantly lower than age 2-11 months; (2) $p<0.01$; variance significantly lower than calm or feeding states; (3) $p<0.05$; variance significantly higher than calm or feeding states; and (4) $p<0.01$; variance significantly higher than lower respiratory tract infection.

COMPARISON OF OBSERVER WITH PNEUMOGRAM RESPIRATORY RATE COUNTS

The differences between respiratory rate counts determined simultaneously by observation and pneumogram were plotted on a scattergram in relation to their mean count for the 60 second counting period, 30 plus 30 second period, and 30 second period doubled (figure). Two outlier observations were excluded from analysis as they were considered technical errors and did not change the values or significance of the differences. The mean difference (SD) was 1.79 (6.85) for the 60 second count, 1.42 (7.21) for the 30 plus 30 second count, and 1.72 (8.60) for the 30 second count doubled. The variance was significantly larger for the 30 second period doubled compared with the 60 second or 30 plus 30 second periods ($p<0.01$).

The influence of age (<2 months, 2-11 months, ≥12 months), child state (calm and awake, feeding, agitated, and sleeping), and diagnosis (lower respiratory tract infection, upper respiratory tract infection, and controls) on the mean difference (SD) of paired pneumogram and observed 60 second respiratory rate counts is shown in table 2. The variability between observed and pneumogram counts was higher for subjects 2-11 months of age than for younger or older subjects ($p<0.01$). The variability between methods was lowest when the counting was done on a sleeping subject and highest when the subject was agitated. The counting during these two states were significantly different from counting when the subject was calm or feeding. There was no significant difference in variability between counting when the subject was calm versus feeding. The variability was also significantly lower when the subject had a lower compared with an upper



Differences between respiratory rate counts determined simultaneously by observation and pneumogram in relation to their mean counts for the different counting periods. The lines represent mean (2 SD). Some points represent more than one observation. Two outliers were not shown.

respiratory tract infection or no respiratory infection (control). There was no significant difference in variability in subjects with an upper respiratory tract infection compared with controls.

COMPARISON OF SEQUENTIALLY OBSERVED RESPIRATORY RATE COUNTS OBTAINED IN THE SAME CHILD STATE

Respiratory rate counts determined by observation during the initial 30 second, 60 second, and repeat 30 seconds of the same counting interval (all within five minutes) were analysed when the child remained in the same state during each counting period. The differences between mean and (SD) were analysed for the 60 second counting periods against 30 plus 30 second and 30 second doubled periods. The mean difference (SD) for 342 paired 60 second and 30 plus 30 second periods were -0.96 (6.5). The mean difference (SD) for 379 paired 60 second and 30 second doubled periods was -0.92 (7.4). The variance was significantly greater between the 60 second and doubled 30 second count (54.8) than the 60 second and 30 plus 30 second (42.25) ($p < 0.01$).

VARIABILITY OF THE RESPIRATORY RATE OVER TIME

The mean (SD) difference in respiratory rates determined by 60 second observed counts between the minimum and maximum rate recorded over the one hour of observation and the 25th, 50th, and 75th centile distribution for the differences are shown in table 3 according to age, state of child, and diagnosis. Taking the whole group, the average difference between maximum and minimum recorded observed respirations was 15.6. Fifty percent had a variation of up to 14 respirations/minute and 75% up to 21 respirations/minute. Variability over time was greatest in (a) subjects between 2–11 months of age, (b) the presence of an upper respiratory tract infection and (c) the agitated state, but the difference in these variances were not significant.

REASONS FOR FAILURES IN COUNTING THE RESPIRATORY RATE

A failure was defined as any substantial interruption in the counting of the respiratory rate that would have rendered the count inaccurate. The distribution of failures in counting by age are tabulated according to counting period, child

Table 3 Variability over time: differences between maximum and minimum respiratory rates in patients counted over one hour of observation

Characteristics	No of subjects	Mean (SD)	Centiles		
			25th	50th	75th
Whole group	97	15.6 (9.9)	9	14	21
Age (months):					
<2	27	15.1 (9.1)	10	17	21
2–11	37	19.9 (11.5)	10	18	25
≥12	33	10.8 (5.6)	7	10	14
Child state:*					
Calm/awake	41	8.2 (7.8)	2	5	14
Feeding	9	7.4 (6.5)	4	6	12
Sleeping	46	7.8 (6.0)	3	6	12
Agitated	31	10.0 (5.2)	7	10	13
Diagnosis:					
Lower respiratory tract infection	20	14.0 (10.3)	9.5	12	13.5
Upper respiratory tract infection	34	17.5 (10.6)	9	15	25
Control	43	14.6 (9.02)	7	16	21

*Some patients were in more than one state over the one hour of observation.

Table 4 Frequency of counting failures according to counting period, child state, and diagnosis. Results are failure/total number of observations (%)

	Age (months)			Total
	<2	2–11	≥12–48	
Counting period:				
1 (60 sec)	26/160 (16)	20/196 (10)	18/170 (11)	64/526 (12)
2 (30+30 sec)	35/169 (21)	24/200 (12)	25/176 (14)	84/545 (15)
3 (30 sec×2)	25/159 (16)	14/190 (7)	10/161 (6)	49/510 (10)
Child state:				
Calm/awake	9/89 (10)	11/188 (6)	14/272 (5)	34/549 (6)
Feeding	6/57 (11)	4/65 (6)	1/12 (8)	11/134 (8)
Sleeping	23/241 (10)	10/174 (6)	3/59 (5)	36/474 (8)
Agitated	18/51 (35)	15/122 (12)	24/125 (19)	57/355 (16)
Diagnosis:				
Lower respiratory tract infection	11/83 (13)	15/159 (9)	13/88 (15)	39/330 (12)
Upper respiratory tract infection	18/62 (29)	18/250 (7)	13/212 (6)	49/524 (9)
Control	32/317 (10)	11/160 (7)	17/197 (9)	60/674 (9)
Total	61/462 (13)	44/569 (8)	43/497 (9)	148/1528 (10)

state, and diagnosis in table 4. Failures were significantly higher (13%) in children less than 2 months old than in those above 2 months of age (8%) ($Z=4.2$, $p<0.0001$).

When the period of counting was taken as a criterion (namely 30 second doubled *v* 60 seconds *v* the sum of two 30 seconds), it was found that there was no significant increase in the overall proportion of failures between the initial 30 second count and 60 second count ($Z=1.03$, $p=0.3$) or between 60 second and the sum of the two 30 second counts ($Z=1.41$, $p=0.16$).

Overall, when the state of the child was considered, it was found that 16% of all observations resulted in counting failures when children were agitated. In contrast, when children were either awake or feeding or sleeping, the failure rate was between 6 to 8% ($Z=5.18$, $p<0.0001$). The presence of respiratory disease did not increase the number of failures. Reasons for failure were agitation (19%), sighing (16%), feeding (14%), crying (13%), observer distraction (9%), yawning (9%), coughing (3%), and others (17%).

Discussion

The primary goal of this study was to determine the most accurate time period for counting the respiratory rate by health workers. Studies of respiratory rate during infancy have used continuous electronic monitoring,^{3 6-8} auscultated counts,⁴ and observed counts.^{9 10} This work has been previously reviewed and we knew of no work that has compared observed and pneumogram counts or the effect of different counting time periods.¹¹ In this regard, the first question that we attempted to answer was which of the three counting periods has the lowest variability when the patient's respiratory rate was measured by both observation and a pneumogram. In this analysis, the most accurate method had the least variability between the observed and pneumogram counts. We are not assuming that the pneumogram is more accurate than observations. Variability between observer counts and pneumogram counts was lower when the sum of two 30 second respiratory counts or 60 second counts were used relative to doubling a 30 second count.

It was recognised that the major factors that increased variability between a pneumogram and observed count was age between 2-11 months, an agitated state, and an upper respiratory tract infection. The variability was lowest in sleeping subjects and those with lower respiratory tract infections. Possible reasons are that children with lower respiratory tract infections had (a) more rapid respirations, (b) the presence of lower chest wall indrawing, and (c) less activity than controls.

The study found a range of variability of respiratory rate counts obtained over one hour of observation from 10.8 to 19.9. However, our study was not designed to determine the impact

of this variability on the usefulness of respiratory rate thresholds to identify pneumonia in subjects with and without respiratory symptoms. The possibility that subjects with pneumonia are more likely to maintain a raised respiratory rate over the WHO threshold compared with other subjects is suggested by the results in table 3. This deserves further study with a larger sample size.

An important factor in determining the optimum method of counting the respiratory rate in children is the number of attempts that must be made before an acceptable count can be obtained. Overall, about 10% of all attempts to obtain a satisfactory respiratory count resulted in a failure. There was no significant difference found in the number of failures that occurred when different counting methods were used. However, there was a significantly higher number of failures in children under 2 months of age and in children who were agitated compared with those who were calm, asleep, or were feeding.

In conclusion, the data from this study suggests that one minute's counting either at a stretch or in two blocks of 30 second intervals is probably the optimum method for counting the respiratory rate, when the child is either awake and calm or when asleep. The respiratory rate taken when the child is in a state of agitation is the least accurate, the most variable, and has the largest number of failures. Consideration should be given to advising that the respiratory rate should not be taken in this state.

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Asthma severity at night during recovery from an acute asthmatic attack

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Abstract

This study was undertaken to investigate the severity of night time asthma in children in hospital recovering from an acute attack of asthma. Twenty two children aged 5-14 years were studied. Coughing 'epochs' overnight varied from one to 156 (median 39.5) and mean overnight arterial oxygen saturation (SaO_2) from 82 to 98% (mean 91.3). $\log_e$ values for cough showed a correlation with SaO_2 . An SaO_2 of <90% was invariably associated with coughing but SaO_2 above 95% did not preclude cough. Peak flow measured in the morning or evening correlated with SaO_2 but not with $\log_e$ cough, and clinical examination scores showed no correlation with overnight measurements. Night time SaO_2 correlated better with daytime tests of lung function than $\log_e$ cough. In general, night time indices of severity reflected daytime pulmonary function status but night cough was sometimes prominent in less severely affected cases. At the time of discharge, clinical indices of severity underestimated the degree of functional impairment at night.

Nocturnal symptoms, especially cough, are common and sometimes dominant features of asthma in children. Control of symptoms tends to deteriorate at night¹ and in adult asthmatics respiratory crises and death are more common at this time.^{2,3}

In children, nocturnal symptoms are often under reported,⁴ suggesting that night time morbidity may be underestimated. In a study of asthmatic children with prominent nocturnal symptoms, Thomson *et al*⁵ demonstrated that cough is most frequent during the two hours after retiring and again before getting up in the morning, and not between 3 and 5 am when peak flow is lowest.⁶ This has led to speculation about the relationship between night cough and wheeze in asthma⁷ and the interrelations of various measures of night time severity. The relationship between indices of night severity and daytime pulmonary function status, recently reported for adults,⁸ has similarly received little attention in children.

This study investigated the interrelation of night cough, overnight arterial oxygen saturation (SaO_2), evening and morning peak flow, and the relation of each to day time indices of lung function in a group of children about to be discharged from hospital after an acute attack of asthma.

Patients

Twenty two patients were recruited from the paediatric wards of the Leicester Royal Infirmary over an 18 month period. Those eligible for the study were schoolchildren (5-14 years) admitted for at least two nights with an acute asthmatic attack. As most asthma admissions in this hospital stay only one night, selection was biased towards those with more severe or prolonged attacks for whom hospital stay (including the days of admission and discharge) varied from three to five days (mean 3.5). The availability of staff and equipment were further constraints on patient selection. Thus if two or more children were suitable for study on the same night, one was chosen at random. The study was approved by the Leicester Health Authority ethical committee.

The children selected had a history of episodic wheezing and had demonstrated an increase in peak flow exceeding 15% after inhalation of a β_2 agonist. On admission to hospital they had extremely low or unrecordable peak flow readings but were competent at using a peak flow meter when well. Children entered the study on the day before planned discharge. Participation did not influence clinical management or decisions about the timing of discharge.

All had been treated with two hourly nebulised β_2 agonists and oral prednisolone (2 mg/kg/day) at the time of admission to the study. Two children also received intravenous aminophylline and hydrocortisone when the initial response to treatment was poor. When suitable patients had been identified, the nature of the study was explained to the parents and the child and informed consent was obtained. Details of the current admission and past history were obtained from interview with the parents and from previous medical records (table 1). Most attended the hospital as outpatients on a regular basis but five had not been admitted previously. At the other extreme, one 7 year old child had 25 documented asthma admissions, including four in the previous 12 months. All but one had received regular treatment at home and 15 were on prophylactic sodium cromoglycate or beclomethasone.

Methods

Lung function tests were carried out on the afternoon before overnight monitoring. Lung volume and airway resistance were measured by whole body plethysmography (Bodytest, Jaeger Ltd), maximum expiratory flow rates by an electronic spirometer (Gould) and peak flow with a Wright peak flow meter. All measure-

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Table 1 Details of study children

Age (years)	
Mean	9.0
SD	3.0
Range	5.2–14.4
Height (m)	
Mean	1.31
SD	0.17
Male:female ratio	15:7
Highest respiratory rate	
Mean	48
SD	12
Range	32–80
Intravenous medication	2
Length of stay in days	
Mean	3.5
Range	3–5
Previous admissions	
Mean	4.4
SD	6.3
Range	0–25
Regular medication	
Nil	1
β_2 agonist	21
Sodium cromoglycate	7
Inhaled steroid	8
Symptoms at home	
Intermittent	12
Continuous	10

ments were made before and 10–15 minutes after inhalation of salbutamol. The results (except residual volume (RV) as a ratio of total lung capacity (TLC) were converted to percentage of the predicted values for height using published data on normal children^{9–13} to facilitate comparison between children of different ages. Daytime (awake) SaO_2 was measured in the late afternoon over at least 10 minutes, with the child resting and supine using the system employed for the night study.

Clinical examinations were carried out by one clinician (EWH) before each overnight monitoring and again the next morning. Pulse rate, respiration rate, blood pressure, and pulsus paradoxus were recorded. A subjective score (0–2) was given for hyperinflation, tracheal tug, intercostal recession, audible wheeze, and auscultatory wheeze. Peak flow was also measured at these times.

Overnight monitoring was done in a quiet cubicle adjacent to the ward area. A Biox 3700 Pulse Oximeter attached to a Squirrel data logger (SQ32–3V/IL/3D, Grant Instruments Cambridge Ltd) monitored SaO_2 and pulse rate (averaged over three seconds) at one minute intervals. A finger probe was secured firmly using adhesive tape and remained in situ overnight. The stored overnight data were examined to exclude any artefact due to a poor probe position and body movement. As the pulse rate was also recorded, this consisted of excluding SaO_2 readings associated with a sudden inappropriate fall in pulse rate. These exclusions comprised only a small fraction of each overnight record, and although these points were excluded from analysis, the large number of data points through the night meant that they would have had little discernible effect on the mean SaO_2 . The results were analysed to give mean SaO_2 and percentage time $<90\%$ SaO_2 .

Night cough was recorded on a tape recorder

using a cough monitor with a voice activated switch set at a selected trigger level, as described previously.⁵ The two microphones were mounted on freestanding tripods placed on either side of the bed, pointing towards the subject and adjusted so that coughing from any part of the bed would activate the switch. A BBC computer and specially designed programme facilitated analysis by giving the number of 10 second 'epochs' during which coughing occurred. This method gave qualitatively similar results to counting individual coughs. The extraneous noises that occasionally occurred were excluded from the analysis by listening to each tape during the analysis procedure. These were easily detected and there was no evidence that they disturbed the children or provoked them to cough.

Results

The children were discharged home on the day after the overnight study, except for one who continued on nebulised salbutamol for a further 24 hours before discharge. Treatment with inhaled bronchodilator and oral prednisolone continued at discharge. Other medication was continued as before admission.

NIGHT TIME MEASUREMENTS

Table 2 summarises the results for the night time measures of asthma severity. The number of coughing epochs throughout the night varied from 1 to 156 with a median value of 39.5 and a mean of 49.3. The data were normalised by taking $\log_e$ values.

The mean overnight SaO_2 for the group as a whole was 91.3% and the mean percentage time less than 90% saturation was 35.9%. Seven children had $\text{SaO}_2 <90\%$ for more than 50% of the time and three for more than 90% of the time. The difference between maximum and minimum overnight SaO_2 recordings ranged from 5 to 21% with a mean of 14.5%. On examining the individual SaO_2 traces, baseline values were remarkably constant during the night, with no evidence of change with time and no evidence of prolonged periods of desaturation. Figure 1 shows a typical overnight oxygen saturation trace and figure 2 a comparison of two methods of presenting the data obtained.

The mean percentage of predicted peak flow for evening and morning for the cases where paired results were recorded was 69% and 67% respectively (SE of the mean difference = 5.0). Six children out of 16 and five out of 19 studied in the evening and morning respectively had a peak flow $<80\%$ of the predicted value. The mean peak flow variability (expressed as the

Table 2 Night time measures of asthma severity

Parameter	Mean	Range
Coughing epochs	49.3	1–156
Overnight mean SaO_2 (%)	91.3	82–98
Evening PF as % of predicted value	72.3	31–129
Morning PF as % of predicted value	66.7	27–110
PF variability %	–7.1	–71 to +38
Evening clinical score	3.2	0–7
Morning clinical score	2.4	0–5

Peak flow (PF) variability is calculated as $(\text{PF}_{\text{pm}} - \text{PF}_{\text{am}}) / \text{PF}_{\text{pm}} \times 100$.

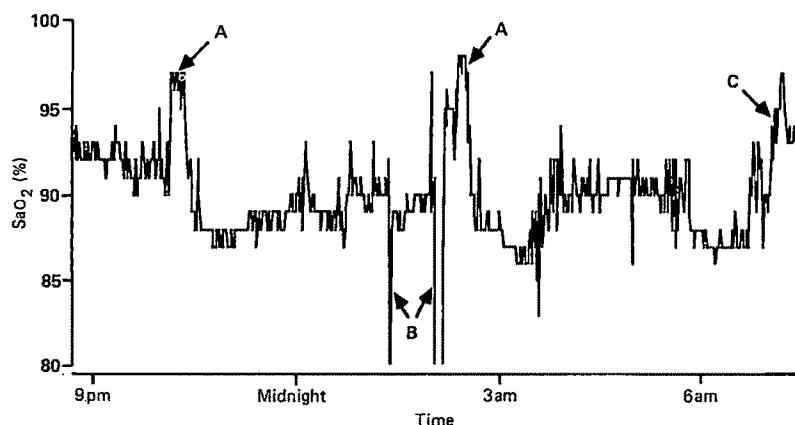


Figure 1 Typical overnight SaO_2 trace. Mean saturation for this case was 90%. At points marked A, nebulised salbutamol was given. At B, the drop in saturation was associated with a sudden drop in pulse rate, indicating poor connection of the finger probe. At C, a further nebuliser was given and the child woke up. Recordings at all these points were excluded from analysis.

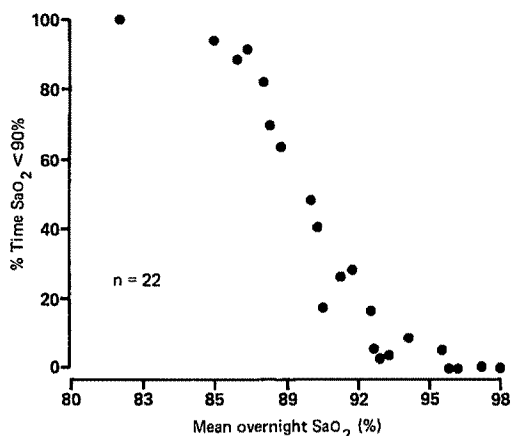


Figure 2 Duration of low SaO_2 compared with mean overnight SaO_2 .

Table 3 Pearson correlation coefficients for night time variables

	Log_e cough	Mean night SaO_2
Mean night SaO_2	0.564*	—
Evening PF	-0.324	0.578*
Morning PF	-0.257	0.481*
PF variability	-0.341	0.108
Evening clinical score	-0.111	-0.117
Morning clinical score	-0.107	-0.235

* $p < 0.05$.

PF, peak flow.

percentage change in peak flow between evening and morning) was -7.1% (SD=36, pre-bronchodilator data).

The clinical assessment in the evening (maximum score=10) was mean 3.2, and the next morning was mean 2.3 (SE of the mean difference=0.32, $p < 0.05$).

CORRELATION OF NIGHT TIME VARIABLES

The data are shown in table 3. There was a significant negative correlation between overnight log_e cough and SaO_2 ($r = -0.564$, $p = 0.01$, see fig 3) but no correlation between log_e cough and any of the peak flow measures. There was a significant correlation between mean overnight SaO_2 and both evening and morning peak flow.

Neither evening nor morning clinical scores correlated with log_e cough, night SaO_2 or peak flow.

NIGHT TIME AND DAYTIME MEASUREMENTS

The mean daytime SaO_2 was 93.0% (range 89.0–96.5%).

Table 4 gives the results of lung function tests. They show varying degrees of hyperinflation and expiratory airflow limitation within the group.

There was a small but not significant difference between daytime and overnight SaO_2 .

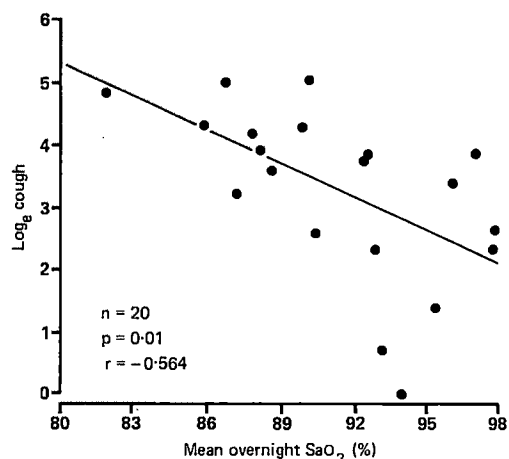


Figure 3 Comparison of overnight cough and overnight SaO_2 .

Table 4 Results of lung function tests

Parameter	Before bronchodilator			After bronchodilator		
	No	Mean	Range	No	Mean	Range
Vital capacity ⁹	17	74	31–124	17	78	42–124
RV ⁹	14	154	72–261	16	143	71–214
TLC ⁹	19	96	70–124	18	95	64–125
Thoracic gas volume ⁹	20	105	69–140	20	101	66–129
RV:TLC ratio	14	41	19–66	16	38	19–60
FEV ₁ ¹⁰	18	72	34–135	19	74	42–135
Forced vital capacity (FVC) ¹¹	15	85	47–133	15	91	53–137
FEV _{0.1} :FVC ¹⁰	18	75	57–96	19	74	57–94
MMEF ¹⁰	13	53	18–108	14	52	17–105
Maximum expiratory flow:						
50% FVC ¹²	15	55	23–118	15	57	25–118
25% FVC ¹²	13	43	10–101	14	39	7–102
60% TLC ¹¹	16	29	74–89	15	39	2–89
Peak flow ¹³	21	72	41–124	21	78	48–129
Airway resistance	21	231	105–504	21	176	63–274

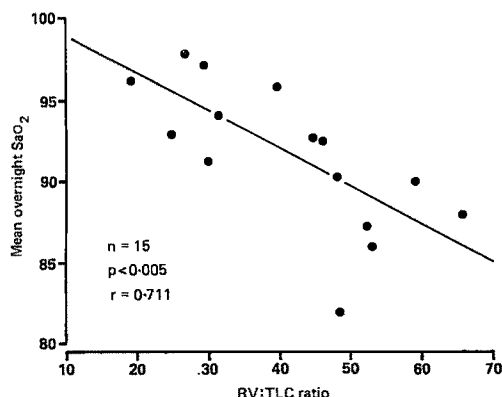
Results are expressed as percentage of the predicted value for height based on published reference ranges, except RV:TLC where the ratio is given as a percentage.

*MMEF, maximum mid-expiratory flow.

Table 5 Pearson correlation coefficients of night time with daytime measures of asthma severity

	Log _e cough	Mean night SaO ₂
Mean daytime SaO ₂	-0.078	-0.585*
Peak flow during day	-0.361	0.520*
RV:TLC	-0.450*	-0.711*
Maximum expiratory flow:		0.720*
60% TLC	-0.378	0.328
50% VC	-0.225	0.330
25% VC	-0.498†	-0.236
Airway resistance	0.245	

VC, vital capacity.

*= $p < 0.05$.†= $p < 0.1$.Figure 4 Overnight SaO₂ compared with the degree of hyperinflation (RV:TLC).

(mean fall = 1.2%, SEM = 0.74, $p < 0.08$) with a significant correlation between the two variables ($r = 0.585$, $p < 0.01$, table 5). There was no correlation between log_e cough and daytime SaO₂.

The overnight SaO₂ correlated best with presalbutamol measures of RV:TLC (fig 4) and the maximum expiratory flow at 60% of TLC and to a lesser extent with peak flow. There was no association of SaO₂ with maximum expiratory flow at 50% or at 25% of vital capacity.

Less marked correlations were found between log_e cough and the results of lung function tests. Log_e cough correlated with RV:TLC but not with the maximum expiratory flow at 60% of TLC or with peak flow. The evening and morning clinical scores also correlated with this hyperinflation ($p < 0.02$, $r = 0.605$; and $p < 0.005$, $r = 0.693$ respectively) but not with expiratory flow at 60%.

Discussion

In this group of asthmatic children, studied before discharge from hospital, there was a high prevalence of pulmonary function abnormalities both by day and night, with wide variation in severity. Although there was an inverse relation between log_e cough and SaO₂ measured overnight, several children coughed frequently despite relatively normal SaO₂ concentrations. Evening and morning peak flow correlated with SaO₂ but not with log_e cough, and peak flow variability did not correlate with either. Clinical scores showed no relationship with any measure of night time asthma. Among daytime measures the degree of hyperinflation correlated best with the night time variables, particularly SaO₂.

These results probably reflect the situation for most children at the time of discharge from hospital after a moderate to severe attack of asthma, as participation in the study had not influenced clinical decisions.

The median cough score (39.5, range 1–156) is much higher in this study than that reported for asthmatic children of similar age with persistent night cough studied at home, in whom median cough score was 6.6 episodes per night (range 0–272).⁵ It is also higher than the reported mean value of 14.6 episodes in adult patients with chronic bronchitis and persistent cough,¹⁴ although a different definition of a coughing episode was used. Higher median cough counts were obtained for adults admitted with acute respiratory problems¹⁵ but comparisons are difficult as these authors counted individual coughs.

This group also showed a high prevalence of hypoxaemia with eight out of 22 children having mean SaO₂ < 90%. Our method of collecting the SaO₂ data used lower sampling rates than other studies and did not allow us to look for dips in saturation associated with coughing bouts, but studies in adult patients suggest that dips in SaO₂ are strongly correlated with sleep state and not at all with episodes of coughing.¹⁴ Coughing often involves quite extensive body movements so dips during coughing may be difficult to interpret. SaO₂ normally decreases slightly at night and that fall is larger in asthmatic children.^{16, 17} The mean range of SaO₂ through the night for our patients was 14.5%, which compares with 5.1% and 6.8% for clinically stable asthmatics^{16, 17} and 8.9% for those on suboptimal treatment.¹⁷ All the individual measurements of SaO₂ were associated with a consistent recording of the pulse and therefore probably reflect a true increase in the variability of SaO₂ in this group. Although the mean saturation was below 90% in eight cases, all the children were considered fit for discharge the next day.

Evening and morning peak flow were both low with 38% and 26% of children respectively having a peak flow < 80% of that predicted. Mean values were lower in the morning than in the evening, but this effect was not significant. The evening and morning readings and the peak flow variability showed wide variation within the group.

Clinical scoring systems^{18, 19} are partly subjective and difficult to validate, but do attempt to quantify the degree of clinical severity. The relatively low scores seen in this study reflect the fact that the children were considered ready for discharge—a condition of entry to the study. Clearly the scores obtained were poor indicators of functional severity in the children studied.

There was a correlation between overnight log_e cough and mean overnight SaO₂. Children with low SaO₂ had high cough counts but the converse was not necessarily true (fig 3). In a study of night cough in asthmatic children, Thomson *et al* found that most episodes occurred within two hours of going to bed or shortly before waking.⁵ Sleep status was not recorded in this study but electroencephalographic studies

in coughing adults have shown that 85% of night coughing occurs during wakefulness and that coughing rarely wakes patients from sleep.¹⁴ There was no evidence of hypoxaemia at the beginning or end of the night in this study, which makes a causal relationship between cough and hypoxaemia unlikely. The distribution of cough receptors in the airways and lungs has been the subject of a recent review.²⁰ It seems probable that during acute attacks of asthma the mechanisms responsible for airway narrowing and cough may to some extent overlap. There was, however, no association between log_e cough and peak flow. Cough occurs mainly at the beginning and end of sleep,⁵ whereas the nadir of peak flow is at around 4 am.^{6, 21} This may reflect differences between the pulmonary mechanisms in cough and airflow limitation. It has been shown that increased bronchial responsiveness is present in adult asthmatics whose predominant symptom is cough²² or marked variability in peak flow.⁸ Conversely, there is evidence that children with chronic cough have similar family histories and atopic characteristics to those of children with asthma,²³ and bronchial hyperresponsiveness which responds to theophylline.²⁴ These studies suggest that in such cases cough is best treated with bronchodilators.²²

There was a correlation between evening and morning peak flow and nocturnal SaO₂ though the behaviour of individuals was not predictable. Previous studies^{6, 17} in asthmatic children between acute attacks have shown no correlation between mean nocturnal SaO₂ or SaO₂ drop and degree of obstruction measured as forced expiratory volume in one second (FEV₁) but one study¹⁷ showed a correlation between maximum fall overnight of SaO₂ and maximum change in FEV₁. Hypoxaemia persisting after reversal of airflow obstruction merely reflects persisting ventilation/perfusion imbalance in the lungs.

The clinical assessment did not predict either night cough or SaO₂. Clinical indices of severity correlate poorly if at all with arterial oxygen tension in the acute attack.¹⁸ Our clinical assessments underestimated night time functional severity to a considerable extent.

In general, both overnight log_e cough and SaO₂ showed similar correlations with day time tests of lung function, but the relationship with night SaO₂ was always closer. In contrast to adult asthmatics with prominent cough²² there was little evidence in this study that those with more coughing had greater large airway involvement (as measured by peak flow or airway resistance). Increasing RV:TLC was the best single marker of poor night time function, correlating well with high cough rates and a low SaO₂. It is a measure of hyperinflation and, by implication, peripheral airways obstruction, which in turn influences ventilation/perfusion ratios. However, the association is not necessarily causal and in the case of cough is unlikely to be so. In children, the normal range for the hyperinflation ratio²⁵ is 22%+8% and only two in this study group were within the normal range. This ratio also correlated with the clinical score, in contrast to the findings in an out-

patient study which showed no association between clinical examination and lung function abnormalities.²⁶ Although flow rates at low lung volumes (50% and 25% of vital capacity) showed no association with SaO₂, once this was corrected for the degree of hyperinflation (60% of TLC) a significant correlation emerged. Thus, reduced flow rates were also a good marker for low nocturnal SaO₂ but only if corrected for the degree of hyperinflation.

As cough, expiratory airflow limitation, and hypoxaemia are all features of severe asthma, some correlation between these variables is to be expected. Night cough is certainly a feature of severe dysfunction in asthma, but can be a persistent symptom in its absence. Its inter-relationship with wheeze needs further investigation.

We are indebted to Fisons PLC who gave generous support for DMH.

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Effect of controlled release salbutamol on nocturnal cough in asthma

E W Hoskyns, A Thomson, E Decker, A Hutchins, H Simpson

Abstract

Sixteen asthmatic children completed a double blind placebo controlled crossover study of controlled release salbutamol (CRS) to assess its efficacy in controlling night time cough. Children with asthma were enrolled into the study on the basis of a history of persistent cough confirmed by two overnight tape recordings at home. Outcome was measured by two overnight tapes on each medication. Other treatment was unaffected. There was no significant fall in cough counts on CRS. Median scores were 14.5 and 12.0 coughing episodes per night for CRS and placebo respectively. Mean overnight oxygen saturation was identical in both treatment periods but morning peak flow showed a trend towards improvement on CRS. Treatment with CRS does not have a significant effect in control of night cough although it may improve objective measurements of lung function.

Cough, particularly at night, is a major symptom of asthma. Although wheeze is a hallmark of asthma, cough may be the more prominent symptom. The relationship of cough and wheeze in asthma and the underlying mechanisms involved have not been fully elucidated.¹ Night cough in asthma may reflect diurnal variation in peak flow² but the timing of coughing episodes³ does not necessarily coincide with that of minimum peak flow. Another possible explanation for increased symptoms at night is that daytime medication with short acting inhaled bronchodilators is insufficient to control night time symptoms.

Oral controlled release salbutamol has been marketed as having a place in control of night time asthma. Twice daily dosage of 4 or 8 mg tablets provides a smooth plasma profile⁴ and comparison of controlled release salbutamol (CRS) with oral theophyllines has shown the preparations to be equally effective in adult asthma.^{5,6} Preliminary results in children gave similar results.⁷ These studies have also shown that CRS is well tolerated with fewer adverse effects.

The aim of this study was to ascertain the effectiveness of CRS in asthmatic children with persistent night cough.

Subjects

Twenty seven children aged 6-14 years with moderate to severe asthma who attended the children's chest clinic at Leicester Royal

Infirmary on a regular basis were considered initially for enrolment into the study. The diagnosis of asthma was made on the basis of clinical findings and the demonstration of reversible airway obstruction (>15% increase in peak flow after inhalation of salbutamol). The children were considered for the study if, in addition, there was a history of persistent night cough (of several months' duration) not controlled by current medication or associated with a recent upper respiratory infection. Although cough is a common feature of asthma, persistent cough was uncommon in patients attending the clinic and recruitment took a period of two years. Children already receiving theophylline preparations, long acting β_2 agonists, or oral steroids were excluded, as were those with concurrent chronic systemic disorders.

Methods

EQUIPMENT

The system for recording nocturnal cough has been described previously.³ Essentially it consisted of a directional microphone placed near the child's bed connected to a UHER 4200 tape recorder with a voice activated switch. An acoustic delay ensured that the activating noise was recorded at operating speed by the tape recorder. Ten seconds after cessation of coughing the tape recorder stopped and the time of the episode was recorded on a second channel. The switch threshold was adjusted individually for each child before monitoring. The tape was analysed aurally to exclude extraneous noises and by a specially designed computer program to give the number of 10 second coughing episodes. As the cough counts have a skewed distribution, statistical comparisons were made using log_e cough counts.

Overnight arterial oxygen saturation (SaO₂) and pulse rate (averaged over three seconds) were recorded at one minute intervals using a Biox 3700 pulse oximeter attached to a Squirrel data logger (SQ32-3V/IL/3D, Grant Instruments Cambridge Ltd). The finger probe was firmly attached to the child with tape. The overnight data were then edited to exclude any episodes of poor probe connection and the mean overnight saturation calculated.

Each child was given a Wright mini peak flow meter to use at home. Other lung function tests were performed in the respiratory laboratory. Lung volumes and airway resistance were measured in a whole body plethysmograph (Jaeger Ltd) and expiratory flow rates by an electronic spirometer (Gould). Measurements were made

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before and after inhalation of bronchodilator and all results were converted to percentage predicted for height using standard published data.

TRIAL DESIGN

The trial consisted of one week run-in period followed by a double blind crossover with one week each of CRS 4 mg (Volmax, Glaxo UK) or placebo twice daily. During the run-in period placebo tablets were taken and the child asked to complete a standard diary card (with grades 0-3 for severity of symptoms of wheeze, day and night cough, exercise tolerance, and nasal symptoms) and twice daily peak flow recordings (7-8 am and 7-10 pm) using the Wright mini peak flow meter. During the week the child attended the lung function laboratory for assessment of lung function. On days 6 and 7 of the run-in week, the family were visited at home and overnight recordings of cough and Sao_2 were made. At the same time the diary card was checked for completeness and inquiries made about compliance with medication and ability to swallow the tablets whole. If the child had completed the diary card, had taken the placebo satisfactorily, and had recorded at least 20 coughing episodes over the two nights, he/she was entered into the crossover phase.

Diary card requirements, peak flow, and overnight monitoring (cough, Sao_2 , and heart rate) in the second and third weeks were the same as for the run-in week; during this period each child was randomised to receive either CRS or placebo first. Deterioration in the control of asthma resulting in the prescription of oral steroids or admission to hospital was regarded as a treatment failure and the child withdrawn from the study. The Leicester Health Authority ethical committee approved the study and informed consent was given by parents before enrolment.

SAMPLE SIZE

The main outcome indicator of the trial was change in night cough. As the number of coughing episodes was not normally distributed it was expressed as $\log_e$ cough. Using the SD of $\log_e$ cough values from previous studies in similar children of 0.72 (unpublished observations), nine children would be needed to show a 50% reduction and 15 children to show a 45% reduction in number of coughing episodes, assuming a power for the study of 80%.

Results

Sixteen of the original 27 children completed the study. The 11 failures were excluded at the end of the run-in period. Six children did not meet the entry criteria of >20 coughing episodes over two nights, and five did not fill in the diary cards satisfactorily. None was withdrawn on medical grounds.

Table 1 gives details of the children who completed the study. All were being treated with short acting inhaled β_2 agonists and 13 were also receiving inhaled steroid medication. Lung function tests reflect the range of daytime

Table 1 Details of children studied. Results are mean (range) except where stated otherwise

Age (years)	9.3 (4.8-14.0)
No of boys	10
No on medication	
Inhaled bronchodilator	16
Inhaled steroids	13
No with atopic symptoms	
Eczema	10
Rhinitis	9
Conjunctivitis	4
Urticaria	4
Diary card scores	
Night cough	1.3 (0-2.5)
Night wheeze	0.75 (0-3.0)
Nasal symptoms	0.66 (0-2.0)
Daytime symptoms	0.92 (0-2.7)
Lung function	
Forced expiratory volume ($\text{FEV}_{0.75}$)	92 (26-125)
Forced vital capacity (FVC)	99 (57-120)
FEV_1/FVC	77 (38-98)
Peak flow	92 (23-141)
Airway resistance	204 (82-748)
RV:TLC	35 (18-72)

$\text{FEV}_{0.75}$, FVC, FEV_1/FVC , peak flow, and airway resistance are expressed as % predicted for height and residual volume total lung capacity (RV:TLC) as a ratio for which the normal range is approximately 22% $\pm$ 8.

severity in children attending the outpatient chest clinic.

RUN-IN PERIOD

Mean peak flow during the run-in week was 95.9% (evening) and 89.2% (morning) with mean overnight variability (percentage change from evening to morning) 7.1%. Symptom scores (median per day on a scale of 0-3) during the run-in week were: nocturnal cough 1.5, wheeze 0.75, limitation of activity 1.75 and nasal symptoms 0.25. On overnight monitoring the median number of coughing episodes per night was 25.5 (range 13-195) and mean Sao_2 95.1%.

CROSSOVER PERIOD

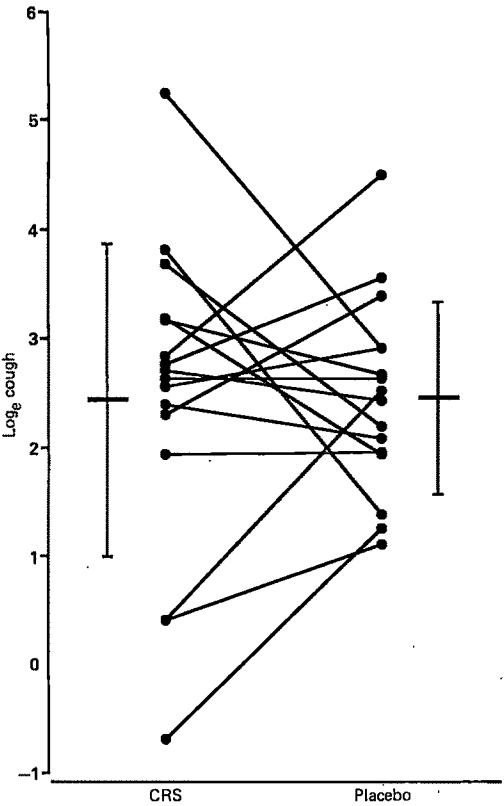
Seven children (44%) received CRS first and there was no significant order effect for any of the variables measured. There was no significant improvement in $\log_e$ cough with CRS (figure). In absolute numbers there was an increase in median cough counts on CRS from 12.0 to 14.5. The $\log_e$ cough scores were almost identical (table 2), with confidence intervals for the difference equivalent to -2.0 to +1.9 coughing episodes per night. The diary card cough score showed a deterioration of night cough on CRS (>0.05). There was also a deterioration of nasal symptoms on CRS. Sao_2 saturation was not affected (mean=95.8% on both CRS and placebo). Mean peak flow (evening and morning) improved during the treatment week, the increase in morning peak flow on CRS being greatest ($p=0.07$). Mean peak flow variability overnight on CRS was not significantly reduced. The overnight pulse rate was significantly raised on CRS (mean=88 beats/minute compared with 76 beats/minute on placebo, $p<0.003$). On examining the individual paired results, all the children had a higher pulse rate while on CRS.

$\log_e$ cough correlated with parental scoring of night cough ($r=0.588$, $p<0.02$) during the CRS week but not on placebo. Likewise, there

Table 2 Effect of treatment on outcome variables

	Mean CRS	Mean placebo	p Value (SE difference)
Coughing episodes (median)	14.5	12.0	0.99
Log _e cough	2.468	2.464	0.82
Diary card scores			
Night cough	1.2	0.72	0.05
Night wheeze	0.84	0.63	0.48
Nasal symptoms	0.94	0.59	0.09
Mean night SaO ₂ (%)	95.8	95.8	0.82 (0.3)
PF evening as % of predicted value	103	100	0.38 (3.6)
PF morning as % of predicted value	102	94	0.07 (3.8)
PF variability as %	1	5	0.21 (2.9)

Coughing episodes and diary card scores were compared using the Wilcoxon signed rank test, and log_e cough, mean night SaO₂, and PF measurements using a Student's paired *t* test. PF, peak flow.



Comparison of log_e cough on controlled release salbutamol (CRS) and placebo. The vertical bars indicate mean (SD).

was a correlation between log_e cough and peak flow ($r = -0.522$, $p < 0.04$ morning and $r = 0.726$, $p = 0.001$ evening) but only during the treatment week. There was no correlation between log_e cough and either peak flow variability ($r = 0.18$) or mean SaO₂ ($r = 0.29$).

Discussion

In asthmatic children with nocturnal cough as a major symptom uncontrolled by inhaled medication, CRS has no significant effect. The broader than expected range of coughing episodes, particularly in the treatment group (SD for log_e cough = 1.44), reduces the power of the study but the lack of any trend towards improvement makes it unlikely that larger numbers would have shown a different outcome. The uniform increase in pulse rate, the trend to

improvement in morning peak flow, and the good diary card documentation suggest that compliance with medication was satisfactory.

No previous studies have investigated the effect of CRS on night cough. However, other studies have shown that there is no difference between CRS and oral theophylline in terms of peak flow, lung function tests, and symptom scores measured during the daytime.^{5,6} These studies were performed on adult patients with asthma or chronic bronchitis and neither included a placebo group. An unreviewed report of a similar trial in children showed no advantage of CRS over theophylline except that there was a small improvement in the morning and evening peak flow.⁷ Adverse effects were more common with theophylline. In our study there were no reported adverse events or withdrawals related to medication.

One further unreviewed report in children showed a significant improvement in morning and evening peak flow (16.3% and 21.5% respectively) on CRS but was not placebo controlled.⁸ Our study showed mean morning and evening peak flow to be higher on CRS. The difference approached significance for morning values. The study was not designed to show change in peak flow and, with wide SDs, larger numbers would be needed to confirm a significant difference. Improvement in morning peak flow but not in night cough suggests that bronchoconstriction and cough are not directly related in this situation.

Diary card scores of night cough correlated with cough counts but, as shown previously,⁹ these are a poor guide in individual cases. The deterioration in reported cough on CRS is not easy to explain. The association of log_e cough with peak flow in the treatment group but not in the placebo group is probably related to the wider variation in coughing frequency in the former group, making a weak correlation more apparent.

This group of children was chosen because cough was a predominant symptom of their asthma. The severity of asthma varied as measured by peak flow and other lung function tests during the day. The severity of asthma did not correlate with the number of coughing episodes at night for any of these parameters. CRS in the form of Volmax is not an effective treatment of night cough in asthma, even when it results in improvement in peak flow. This supports previous evidence that cough and

airway narrowing are to some extent independent manifestations of asthma in children with both symptoms.

We are grateful to Allen and Hanbury Ltd for providing Volmax tablets and placebo and for funding of ED and AH.

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Now for chickenpox

Chickenpox is the last of the great traditional childhood infections to remain untrammelled by vaccination. Although usually fairly benign it can and does cause much trouble, often disrupting paediatric medical and surgical wards because of its infectivity. It is a cause of severe embryopathy, encephalitis presenting particularly as acute ataxia, and severe disease in the very young and the immunocompromised. We could well manage without it. In the last five years live varicella vaccines have been licensed in Japan, Korea, and several European countries. Now a similar vaccine produced by Merck Sharpe and Dohme has been tested on over 3000 children in America (C Jo White and colleagues, *Pediatrics* 1991;87:604-10).

Adverse reactions were relatively few. One child developed a fever and a swollen knee 16 days after the vaccination. Mild problems at the injection site, usually pain in the first three days, were experienced by 13% of children. Four percent developed a rash confined to the injection site and a further 4% had a varicelliform rash, which was usually mild, occurring at about 14 to 25 days after injection. Viral culture was attempted in 32 cases of post vaccination varicelliform rash and varicella zoster virus was isolated from 11. Nine of these isolates were typed by restriction endonuclease analysis and eight were shown to be wild virus and not the vaccine strain. Which just goes to show, you can't assume nut'n. Less than 1% of vaccinees had a fever of more than 38.9°C within three days and the incidence of fever in the six weeks after vaccination was no greater than might be expected in normal children.

Ninety six percent of vaccinees showed seroconversion at six weeks and all the non-responders given a second dose showed seroconversion after that. Antibodies persisted at one year in almost all cases. The vaccine showed an 86% efficacy in preventing chickenpox in household contacts in the first year after vaccination and when the disease occurred it was usually mild, the mean number of lesions being 32 compared with about 500 in natural chickenpox. Two mild cases of shingles have been reported in earlier trials of varicella vaccine but the incidence of shingles after vaccination seems to be no higher than after natural infection. Data from previous trials indicate that humoral immunity persists for at least four years. It will be necessary to continue to collect data on the persistence of immunity and the possible need for revaccination but the prospects for control of disease due to varicella zoster virus look good.

Next on the list must surely be respiratory syncytial virus. And then what shall we do in the winter time? Now Jonah, be quiet. What do you mean 'When we got rid of smallpox we got AIDS. When we get rid of chickenpox . . .?' Now that's no way to think, is it?

Prediction of blood pressure from plasma renin activity in reflux nephropathy

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Abstract

As there is a 10% risk of hypertension developing in children with reflux nephropathy and the renin-angiotensin system has been implicated in its aetiology, a long term prospective study has been undertaken to explore the relationship between plasma renin activity (PRA) and blood pressure in such patients. In 1978, of 100 normotensive children with reflux nephropathy 8% were shown to have PRA above normal. Five years later of 85 subjects suitable for analysis 13% had increased PRA and it was shown that PRA and blood pressure SD scores significantly increased. The present study refers to the 10 year follow up in which 95 of the original group were traced but eight of these were unavailable for study and 28 others were excluded from analysis because of extraneous factors that might influence blood pressure or PRA. Results therefore on 59 have been analysed. PRA was above normal in 13/59 (20%) subjects, and PRA and blood pressure SD scores had further increased. The data continue to support the role of the renin-angiotensin system in the observed rise of blood pressure in reflux nephropathy, but individual PRA measurements do not appear so far to predict reliably the onset of hypertension in affected patients.

The commonest cause of severe hypertension in childhood is pyelonephritic scarring secondary to urinary tract infection and vesicoureteric reflux.¹⁻³ Hypertension affects at least 10% of these patients and, once present, hypertension can accelerate the deterioration of renal function.⁴⁻⁷ Furthermore, hypertension is associated with considerable morbidity and mortality, which makes early diagnosis and treatment extremely important.⁸⁻¹⁰ The aetiology of the hypertension in these patients is not clear. The renin-angiotensin system has been implicated due to the frequent finding of a raised plasma renin activity (PRA) in hypertensive patients with reflux nephropathy.¹¹

In an attempt to identify the role of PRA as a possible predictor of the development of hypertension in these patients, in 1978 we started a long term prospective study in 100 normotensive children known to have renal scars.¹² At that time 8/100 patients had increased PRA and the natural tendency of PRA to fall with age was less pronounced than in normal controls.¹² Five years later 98 of the initial 100 were reviewed and a significant increase in blood pressure and PRA SD scores was found suggesting that there was a relationship between renin and blood

pressure in these subjects.¹³ The present study concerns the 10 year follow up of this population.

Patients and methods

One hundred children with radiologically identifiable renal scarring and vesicoureteric reflux that had been corrected surgically were studied in 1978. At the five year review, 98 of the original 100 patients were contacted. One patient could not be traced and the other had died with hypertensive encephalopathy. Although all 98 patients were investigated, a number were unsuitable for analysis. Thirteen patients were excluded: 11 because they were taking a hormonal contraceptive pill, one because she was pregnant, and another because she had undergone a nephrectomy.

For the 10 year review we traced 95 patients from the original group. However, only 87 patients were studied due to various factors: three refused to cooperate, four were living abroad, and one was neurologically handicapped after a car accident. Of the 87 reviewed, data on 28 were excluded, in 24 because they were taking a hormonal contraceptive pill and in four because they had had a nephrectomy because of hypertension. Data on 59 patients were therefore analysed. There were 30 male and 29 female patients aged 11-25 (mean 17.4) years. None of the patients were receiving antihypertensive treatment or known to have impaired renal function.

Due to their age most of the patients were no longer under the care of the Hospital for Sick Children and were specifically invited to take part in this third follow up study.

Each patient was asked to attend the Hospital for Sick Children in the morning. After a two hour supine rest, blood pressure was measured with a Dinamap vital signs monitor and with a random zero sphygmomanometer. The observer was always the same. A 1 ml blood sample was taken for measurement of electrolyte and creatinine concentrations and for PRA estimation. PRA was evaluated using a semi-microradioimmunoassay¹⁴ and plasma creatinine concentration by the Jaffé reaction with an autoanalyser.

A urine sample was also obtained and mean sodium excretion calculated from the sodium:creatinine ratio assuming that normal daily creatinine excretion is constant at 132 mmol/kg body weight/24 hours.^{12 15}

Blood pressure results from the three studies were expressed as SD scores standardised against the 1987 Task Force data for blood pressure in normal children¹⁶ and calculated using a computer program.

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Plasma renin activity SD scores were calculated in order to compare the results from the three evaluations. Renin results were logarithmically transformed and SD scores calculated according to the equation:

$$\text{SD score} = \frac{\log \text{PRA} - \text{mean log PRA}}{\log \text{SD}}$$

Where $\log \text{PRA} = \log \text{PRA observed}$, $\text{mean log PRA} = \text{mean log PRA for age}$, and $\log \text{SD} = \log \text{standard deviation}$.

The results on PRA and blood pressure SD scores from the first to the second and from the second to the third studies were compared by paired Student's *t* test.

The degree of renal scarring was assessed from the most recent scanning with dimercapto-succinic acid labelled with technetium-99m available. This was scored as in the original study: normal kidney=0, single small polar scar=1, complete polar destruction=2, and loss of both renal poles or a small shrunken kidney=3. It was not possible to obtain recent renal imaging in all the patients to reassess the degree of scarring, but the patients in whom this was obtained showed no change from the second study.

Results

In the first study in 1978, eight of the 100 patients (8%) had a PRA above the upper limit of normal for age.¹² Five years later, 11 of the 85 patients (13%) studied showed a raised PRA.¹³ In the present study PRA was above the normal range in 12 patients (20%) of the 59 studied (fig 1). Four of these patients had a blood pressure

above the 95th centile and two of them had had a raised PRA in the second study although normal values in 1978. Only three patients showed a high PRA in all studies and only one became significantly hypertensive at the present review.

As in the previous investigations, PRA SD scores were calculated so that we could compare renin results from the various studies. The mean (SE) PRA SD score in 1978 was 0.042 (0.14), in the second study 0.453 (0.13), and in this final evaluation 0.845 (0.14). There was a highly significant increase in PRA SD scores between the first and the second studies ($p < 0.001$) and a significant increase between the second and the third ($p < 0.05$) (fig 2). The patient with a PRA of -3 SD scores below the mean (fig 2) was one of the oldest and had only a minor degree of unilateral scarring (grade 1).

In this third follow up study no significant correlation could be found between PRA and mean sodium excretion, plasma creatinine concentration, or the degree of scarring. Similar results were found before.^{12 13}

All patients were originally normotensive when first studied in 1978.¹² Five years later blood pressure was above the 95th centile in three patients and between the 90-95th centiles in four.¹³ Only one of these seven patients had a high PRA at that time.¹³ Of the original group of 100 patients, one had undergone unilateral nephrectomy due to hypertension at the time of the second study, however, his original PRA determination was within the normal range for age. The group of three patients identified as having hypertension in the second study had all been submitted to unilateral nephrectomies at the latest review. As with the patient who was nephrectomised between the two initial studies, the PRA results were within the normal range five and also 10 years earlier. Although not included in the present analysis, two of these patients remained hypertensive when last

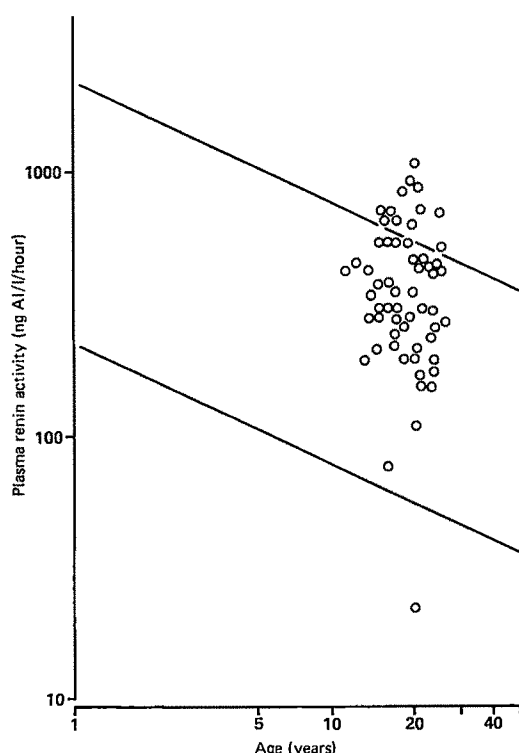


Figure 1 Plasma renin activity in normotensive patients with scarred kidneys in 1988. Solid lines indicate the upper and lower limits of the normal range.

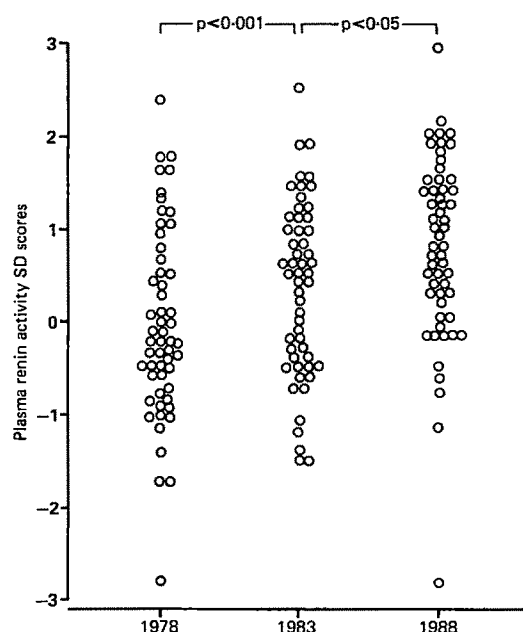


Figure 2 Plasma renin activity SD scores from the initial, five, and 10 year follow up studies.

reviewed, and one had a high PRA while on treatment with a β blocker.

In the present analysis we identified a further eight patients with a blood pressure over the 95th centile and seven with a blood pressure between the 90–95th centiles. However, in only six of these 15 patients was PRA above the normal for age.

As for PRA, SD scores on blood pressure results were calculated in order to be compared. The initial mean (SE) blood pressure SD score was -0.26 (0.22), five years later 0.49 (0.11), and 0.97 (0.12) in this present study. There was a highly significant increase in systolic blood pressure SD score from the first to the second study ($p < 0.001$) as well as between the second and third ($p < 0.001$) (fig 3). A similar observation was found for diastolic blood pressure SD score.

No significant correlation was found between blood pressure and PRA SD scores. We were also unable to find a significant correlation between the variation in blood pressure and PRA SD scores either between the first and second or between the second and third studies.

Discussion

Hypertension is a frequent complication of reflux nephropathy.^{3–5} PRA is often increased in hypertensive patients with this condition.¹¹ When present in these patients, hypertension contributes to further deterioration of renal function.⁷ Therefore an early marker of its onset would be useful in the identification of patients at risk of developing a high blood pressure.

In an attempt to clarify the relationship between blood pressure and PRA in patients with reflux nephropathy, we undertook a long term prospective study. The initial results obtained in 1978 showed that eight of 100 normotensive patients had a raised PRA and we

then postulated that renin could predate, and then predict, hypertension.¹² Five years later only one of the eight patients identified with a blood pressure above the 90th centile had had a raised PRA five years earlier.¹³ Ten years later six of the 15 patients with a blood pressure above the 90th centile showed a high PRA. Furthermore only two of these had an increased PRA in the second review and only one patient with raised PRA in the three studies became significantly hypertensive at the last review. The present results and those from the preceding study do not confirm that isolated PRA estimations can reliably predict the onset of hypertension in patients with reflux nephropathy.

On the other hand the comparison of SD scores for PRA between the first and the last study show a significant increase during the 10 year duration of the study implying that there is a disturbance of the renin-angiotensin system in these patients. Blood pressure SD scores were also significantly increased which confirms that in reflux nephropathy there is a tendency towards high blood pressure and that this may be a delayed event in life.

Interestingly, the three patients identified as hypertensive (with blood pressure > 95 th centile) in the second study, had normal PRA at that stage as well as in the first evaluation but subsequently required unilateral nephrectomies due to severe hypertension. This could be taken as an example of the difficulty in predicting the hypertension development based on renin measurements.

The number of patients taking hormonal contraceptive pills was considerably higher in this third study and led to the exclusion of data from 24 patients from analysis, due to the problems in renin results interpretation in the patients taking these drugs.¹⁷ Of these 24 girls, six had a high PRA and two of these had a blood pressure over the 95th centile for age. Blood pressure was found to be raised also in six girls with normal PRA who were taking the contraceptive pill.

This third study of the same population with reflux nephropathy over a 10 year period continues to support the view that the renin-angiotensin system is abnormal in patients with reflux nephropathy and that this is accompanied by an abnormally high tendency towards high blood pressure. However, individual PRA measurements do not appear, so far, to predict reliably the onset of hypertension in affected patients.

The role of renin as the only determinant of hypertension in reflux nephropathy remains to be established. The study of other factors with a possible role in the aetiology of hypertension in this condition is planned at subsequent follow up studies of this population.

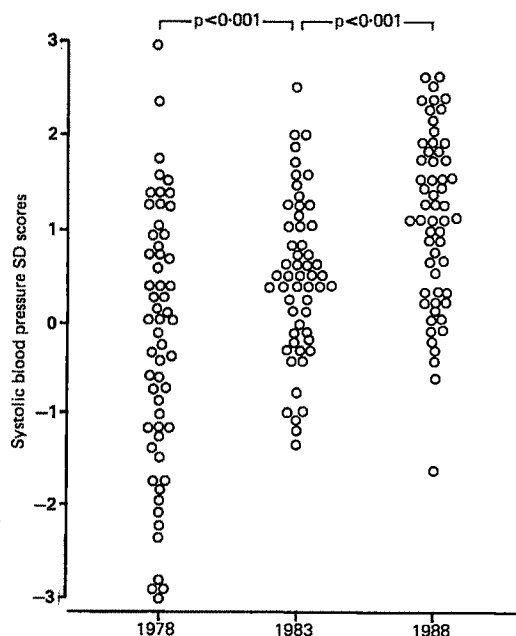


Figure 3 Systolic blood pressure SD scores from the initial, five, and 10 year follow up studies.

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Group A streptococcal exotoxins

When I wrote recently about the reported resurgence of group A streptococcal disease in the United States,¹ I didn't realise that a similar increase had already been described in Britain. In the discussion section of a paper in the *Pediatric Infectious Disease Journal* (Kiran Belani and colleagues, 1991;10:351-4) it is pointed out that in England and Wales the annual death rate from group A streptococcal septicaemia rose from between five and 10 in the early 1980s to between 15 and 22 by the end of the decade. There were about 150 cases a year of group A streptococcal bacteraemia in the second half of the 1970s and 300 a year in the first half of the 1980s. This paper, from Minneapolis, suggests that a change in exotoxin production by the bacteria may be behind the resurgence of severe disease. There are three pyrogenic exotoxins (A, B, and C) produced by group A streptococci, toxin A being the classical erythrogenic toxin of scarlet fever. Toxin A production was common 50 years ago in the heyday of scarlet fever but has been uncommon in recent decades. In the hospital of the University of Minnesota, Minneapolis, six children with severe group A streptococcal disease were seen between 1985 and 1988. One was a 2 week old baby who probably acquired the organism from a sibling with pharyngitis. The other five were aged 3 to 14 years and all had a predisposing condition: two had congenital lymphatic abnormalities, one a recent arm fracture, one eczema, and one chickenpox. (Apparently it is known that severe streptococcal disease may follow chickenpox.) The principal features seen in the six cases were cellulitis, disseminated intravascular coagulation, shock, and gangrene leading to limb amputations in two children. Of the six group A streptococcal isolates three produced exotoxins A and B, one produced B and C, one A only, and one B only. Exotoxin production was shown in 40 of 58 strains isolated from people outside hospital with sore throats but none of those produced toxin A.

It seems that the marked decline in severe scarlet fever which occurred some 40 or so years ago was a result of the loss of the organism's ability to produce toxin A but it appears to have relearned the trick. We'd better watch out.

ARCHIVIST

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Absence from school related to cancer and other chronic conditions

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Abstract
Absence from school during the first year after starting major treatment for cancer or chronic or orthopaedic conditions was examined. Retrospective data were collected on 72 children and obtained from hospital records, school registers, and interviews with parents and teachers. Median initial absences caused by treatment were 91, 29.5, and 15 days for cancer, chronic, and orthopaedic patients respectively. The mean proportions of the remaining school time in the year occupied by absences caused by treatment and those not caused by treatment were respectively 17% and 17% for oncology patients, 8% and 12% for chronic patients, and 2% and 11% for orthopaedic patients. The only significant factor associated with the amount of absence caused by treatment was the type of illness. Increased absence not caused by treatment was associated with the amount of treatment time and the patient being a girl. The proportion of absence not caused by treatment decreased if the mother was educated beyond the age of 18. The possible reasons for and effects of excess absence are discussed.

Research has shown, for at least 30 years, that children with chronic conditions are likely to have up to 50% more absence from school than other children do.¹⁻⁹ It is quite possible that some of these studies are underestimates of the real situation because parental reporting was used. Parents have been shown to under report their child's absence.⁷

Studies of children with specific, as well as general, chronic conditions such as bronchial asthma,¹⁰⁻¹² cardiac problems,¹³ and kidney diseases¹⁴ have also shown that these children miss considerably more school time than their classmates or siblings.

Child cancer patients have only comparatively recently been studied with regard to school, as a greatly improved prognosis has allowed most to return to their education. Many of these children appear to have very high absence rates after their return to school,¹⁵⁻¹⁷ which decrease but are still considerable two¹⁸ or three years¹⁹ after diagnosis.

It is inevitable that children who are chronically ill or who are receiving treatment will miss time from school, but the question arises as to whether or not the quantity of absence is directly related to their condition.

The study described in this paper, which is part of a larger research project on children's

return to school after treatment for cancers,²⁰ funded by the Cancer Research Campaign, attempts to shed light on the reasons which lie behind these excess absences.

Methods
SAMPLE
The sample was drawn from hospitals in the south east and south west of England. The sampling procedure was as follows: all cancer patients aged 4 to 16 years, except those with brain tumours, and those who were not resident in the UK, or who were not fit to return to school, were identified from the hospital and ward lists and entered consecutively into the sample as they reached one year from diagnosis. For each cancer patient, so far as was possible, a matched patient of the same age and sex who had reached one year from the start of major treatment for a chronic or orthopaedic condition was also selected.

Seventy two children for whom complete sets of absence data were available were included in the study. Forty three for whom absence data could not be obtained from the schools were excluded. However, as table 1 shows this loss did not appear to be selective and no bias is assumed.

Their diagnoses included, acute lymphoblastic leukaemia, acute myeloblastic leukaemia, chronic myelocytic leukaemia, Wilms' tumour, non-Hodgkin's and Hodgkin's lymphomas, rhabdomyosarcoma, osteogenic and Ewing's sarcomas, and germ cell tumours.

Table 1 Distribution of sample. Results are number (% of total)

Illness type	Main sample	Subsample
Boys		
Primary		
Cancer	18 (16)	10 (14)
Chronic	11 (10)	5 (7)
Orthopaedic	10 (9)	7 (10)
Secondary		
Cancer	18 (16)	7 (10)
Chronic	7 (6)	4 (6)
Orthopaedic	10 (9)	7 (10)
Subtotal	74 (64)	40 (56)
Girls		
Primary		
Cancer	9 (8)	8 (11)
Chronic	8 (7)	7 (10)
Orthopaedic	6 (5)	5 (7)
Secondary		
Cancer	6 (5)	4 (6)
Chronic	6 (5)	4 (6)
Orthopaedic	6 (5)	4 (6)
Subtotal	41 (36)	32 (44)
Total	115	72

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The chronic diseases included renal failure cardiac conditions, asthma, and others. The orthopaedic conditions included thoracic scoliosis, club foot, trauma, and others. The decision to include thoracic scoliosis and club foot in this group was taken because the treatment pattern more closely resembled that for orthopaedic conditions than for chronic ones.

DATA COLLECTION

The data was collected in the following ways:

- (1) Data on the dates, duration, and nature of treatment were obtained from hospital records, and were recorded in a diary format which enabled inpatient and outpatient treatment and check ups to be distinguished from each other.
- (2) Details for school absences were obtained from the attendance registers in the children's schools.
- (3) Background information was collected by structured questionnaire interviews with the parents and teachers of the children.

Only the 72 children for whom all three sets of data were available were included in the analysis.

All data collection was carried out with the full permission of the relevant ethical committees, consultants, directors of education, head-teachers, and parents.

ANALYSIS OF DATA

The analysis of the data was carried out using the Statistical Package for the Social Sciences (SPSSX).

(1) Amount of absence caused by initial treatment

The length of initial treatment was recorded in days absent from school, *excluding* weekends and school holidays. All absences therefore include only the days on which it would have been possible for the child to attend school but did not. Medians and interquartile ranges were calculated as well as means and SD (table 2).

(2) Amount of absence caused by further treatment after return to school

The mean and SD and the medians and interquartile ranges were also calculated for the following treatments: (a) further hospital inpatient treatment in days, (b) follow up outpatient treatment in days, and (c) follow up outpatient clinic visits for check ups in days.

Table 2 Amount of absence caused by initial treatment: school days absent (number between date of diagnosis and return to school)

Descriptive statistics	Patient group		
	Cancer (n=29)	Chronic (n=20)	Orthopaedic (n=23)
Mean	85.21	37.8	32.9
SD	59.22	31.82	43.5
Median	91	29.5	15
Minimum, maximum	6, 184	2, 120	0, 185
Interquartile range	25, 142	12, 63	8, 48

(3) Proportion of absence caused by treatment after return to school after initial treatment

Because the length of initial treatment absence varied greatly, the amount of time available for attendance at school during the remainder of the year after diagnosis also varied considerably. It was therefore more meaningful to consider the *proportion* of absence by relating the amount of absence to the school time available for attendance.

Dates of school holidays were obtained from local education authorities in the areas studied. The actual possible attendance time for each child was accurately calculated, taking holidays into account, from the date of return to school to the end of the year after diagnosis; this gave the proportion of overall treatment absence (inpatient, outpatient, and clinic check ups).

(4) Patterns of absence caused by treatment

The patterns were examined visually by transferring the diary data to graph paper.

(5) Proportion of absence not caused by treatment after return to school after initial treatment

The same conditions applied to these calculations as to those for absence caused by treatment in (3) above. Absences not caused by treatment were taken to be all those absences recorded in the school attendance registers that were not accounted for by hospital inpatient or outpatient treatments or check ups specifically recorded in hospital records in relation to the disease under consideration.

(6) Background factors related to absences not caused by treatment

These factors, including those identified in the interviews with parents and teachers, were related to the outcome variable. This outcome variable was determined as follows:

$$\text{Outcome} = \frac{\text{Number of non-treatment absence days after return to school}}{\text{Total number of school days}}$$

$$= \frac{A}{B}$$

B consists of two parts, namely, all school days between the date of diagnosis and return to school, plus all school days after the return to school and the end of the observation period. This therefore provides a measure of treatment severity by means of its amount.

One point to consider when modelling this proportion is that the number of days not caused by treatment after the return to school is bounded by the number of school days from the return to school to the end of the observation period. If this latter period of time is only five days long then the maximum number of days absence not caused by treatment possible after the return to school is also five days. In terms of our outcome/dependent variable this particular situation would produce a very low proportion. Hence, only patients who have recorded a reasonable length of time from their return to school to the end of the observation period can be seen as possible frequent absentees.

The background factors included in the regression modelling are shown in table 3.

The findings are, of course, based on a small sample and must therefore be interpreted with caution. Nevertheless much of the research on this topic which has been mentioned earlier in this paper is also on small samples due to the relative rarity of childhood cancers.

Results

(1) Amount of absence caused by further treatment

As table 4 shows, orthopaedic patients had no

Table 3 Background factors recorded

Type of illness
Total No treatment days*
(Total No treatment days)/(total No school days)*
(School treatment days before return to school)/(total No school days before return to school)*
(Total No treatment days)/(total No days before return to school)*
(School treatment days before return to school)/(total No school days)*
(School treatment days after return to school)/(total No school days)*
Sex of child
Primary/secondary school age
Social class
Education: mother/father
Health: mother/father
Presence of home tutor
Desire of child to return to school
Desire of parents for child to return to school
Presence of problems in child reported by parents: physical/academic/psychological/behavioural
Presence of problems in child reported by teacher: physical/academic/psychological/behavioural

*These factors allow disease severity to be reflected in the analysis.

Table 4 Amount of absence caused by further treatment (in school days) after return to school

Descriptive statistics	Patient group		
	Cancer (n=29)	Chronic (n=20)	Orthopaedic (n=23)
Inpatient			
Mean	5.97	5.15	2.04
SD	10.52	14.94	7.08
Median	0	0	0
Minimum, maximum	0, 33	0, 62	0, 33
Interquartile range	0, 9	0, 1	0, 0
Outpatient			
Mean	7.21	0.25	0
SD	8.44	0.72	0
Median	6	0	0
Minimum, maximum	0, 27	0, 3	0, 0
Interquartile range	0, 11	0, 0	0, 0
Clinic visits			
Mean	7.38	6.75	2.52
SD	7.53	6.10	2.31
Median	5	4	2
Minimum, maximum	0, 27	0, 21	0, 8
Interquartile range	2, 11	2, 13	1, 3

outpatient follow up and few admissions to hospital subsequent to the initial treatment. Cancer patients, and to some extent chronic disease patients, can follow a rigorous course of treatment and monitoring. Outpatient treatment for chronic diseases was rare, but admissions as inpatients and check up visits were relatively frequent as they were for cancer patients.

(2) Patterns of absence caused by treatment

When observed graphically three main types of treatment pattern emerged.

(a) One long, or relatively long, treatment followed by regular short absences each usually of one, or a few, days' duration for follow up treatment or monitoring of progress. This pattern was the most frequent one for the cancer patients. Visually the regularity of the single day absences was strikingly clear and was due to the outpatients' clinics attended being held on the same day of the week throughout the year.

(b) Repeated admissions to hospital for relatively short periods from a few days to one or two weeks in length. This pattern was relatively infrequent in this sample of children and was seen for only a few of the cancer patients and some of the chronic cases, such as asthmatics. Most of the patients with other chronic diseases which required surgery, including transplants, followed more closely the pattern described in (a) above.

(c) One long absence with very few subsequent visits to outpatients' clinics. This pattern was most frequent in the orthopaedic cases where, once the condition had been corrected, further treatment and monitoring were largely unnecessary.

(3) Proportion of absence caused by treatment and that not caused by treatment after return to school after initial treatment

Table 5 shows that the cancer patients were likely to lose a greater proportion of their school time in absence caused by follow up treatment than either the chronic or orthopaedic patients. Many of the children had absences from school not directly accounted for by actual sessions of treatment or monitoring.

As table 5 shows, the cancer patients had the highest median proportion of absence not caused by treatment. Chronic and orthopaedic

Table 5 Proportion of absence caused by treatment and that not caused by treatment with respect to possible days back at school

Descriptive statistics	Patient group		
	Cancer (n=29)	Chronic (n=20)	Orthopaedic (n=23)
Caused by treatment			
Mean	0.174	0.075	0.020
SD	0.128	0.104	0.025
Median	0.154	0.027	0.013
Minimum, maximum	0.0, 0.528	0.005, 0.444	0.0, 0.104
Interquartile range	0.067, 0.252	0.016, 0.108	0.005, 0.024
Not caused by treatment			
Mean	0.171	0.115	0.107
SD	0.182	0.106	0.169
Median	0.115	0.104	0.057
Minimum, maximum	0.0, 0.730	0.0, 0.313	0.005, 0.800
Interquartile range	0.035, 0.266	0.010, 0.226	0.024, 0.099

patients after the return to school had more absence not caused by treatment than that caused by treatment.

(4) Factors related to the proportion of absences

The size of sample was not large enough to permit separate analysis of the factors related to each of the three disease groups, therefore the results expressed here related to the absences overall.

(a) *Factors related to absence caused by treatment*—The only significant factor related to increased proportions of absence caused by treatment was the type of condition being treated. Absences caused by follow up treatment for the cancer patients were significantly longer than those of the chronic disease patients ($p=0.001$) and those of the orthopaedic patients ($p<0.0005$). The difference between absences caused by follow up treatment between chronic and orthopaedic patients was less significant ($p=0.02$).

(b) *Factors related to absence not caused by treatment*—As table 6 shows, when the individual background factors were entered into a regression analysis the following associations with the outcome/dependent variable were found:

(i) An increase in the proportion of absence caused by treatment after return to school was associated with an *increase* in the outcome variable, that is, proportion of absence not caused by treatment.

(ii) Patients whose mothers were educated above the age of 18 were associated with a *decrease* in proportion of absence not caused by treatment.

(iii) Girl patients were associated with an *increase* in absence not caused by treatment.

(5) Absence before diagnosis

It seemed reasonable to examine absence during the year before diagnosis, but unfortunately data were available for only 49 children out of the 72. Table 7 shows their prediagnosis absences. They were significantly different ($p=0.01$); this was due to the children with chronic diseases having a mean absence of more than twice as many days in the year than the other two groups had.

With such a reduced sample it was not possible to make a meaningful comparison between absence before and after diagnosis with regard to associated factors.

Table 6 Factors significantly related to absence not caused by treatment (see methods: analysis of data, for equation, p 1218)

Factor	Coefficient	Approximately 95% confidence interval	p Value
Proportion of absence caused by treatment after return to school	0.31	0.16 to 0.45	0.0001
Whether child's mother was educated after 18 years	-0.05	-0.08 to -0.01	0.0082
Female patient	0.04	0.01 to 0.08	0.0135
Constant	0.05	0.02 to 0.07	0.0024

Table 7 Absence in days during the school year before diagnosis (reduced sample for whom data were available)

Descriptive statistics	Patient group		
	Cancer (n=17)	Chronic (n=15)	Orthopaedic (n=17)
Mean	15.12	39.03	18.56
SD	12.68	33.33	18.34
Median	13	27.5	14
Minimum, maximum	1, 50	3, 100	1, 82
Interquartile range	6, 20	8, 70	8, 21

Discussion

On average the cancer patients in this study lost 35%, chronic disease patients 19%, and orthopaedic patients 13% of their available school time in the remainder of the year after their initial treatment. This loss of school time was a combination of absence caused by treatment and that not caused by treatment.

(a) Absences caused by treatment

The tendency now appears to be towards shorter hospital admissions for children.²¹ This present trend permits many children to return to school at the earliest possible opportunity, but makes the need for outpatient treatment or further short admissions to hospital more frequent.

The graphic representation of these absences, especially for the cancer patients, showed that they often fall regularly on a particular day of the week when the paediatric outpatient clinic is held. A previous study showed that this presents problems for some children because they miss the same lessons each time they visit the clinic and thus fall behind in the specific school subjects taught on that day.²² This presented special problems in mathematics²² and, for the younger children, in reading.¹¹ Both these subjects require actual teaching and cannot be caught up by the individual child working alone. It has been suggested that holding paediatric clinics out of school hours would help,¹¹ or calling children to outpatients' clinics on different days of the week if this were feasible for the treatment regimen.

(b) Absences not caused by treatment

Some of the absence not caused by treatment is certainly related to the illness. The proportion of absence not caused by treatment was significantly related to the amount of absence that was caused by treatment. Many child cancer patients on chemotherapy suffer nausea and vomiting after treatment, causing them to miss school.¹⁶ Some also have anticipatory sickness before their treatment. However, the social factors found to be related to the amount of absence not caused by treatment suggest that more than the disease and treatment are responsible for these absences.

(i) *Girls are more likely than boys to have increased absence*—Other studies have shown that girls with cancer¹⁶ and chronic illness⁶ are likely to have more school absence than boys are. This also applies generally.^{13 23 24} It has been suggested that a cultural expectation that

boys should give in to illness less easily than girls might have something to do with this difference.¹⁶ There is evidence that girls' attitudes to health do differ from those of boys. For example, girls were significantly more likely to pay attention to pain, to express fear of getting hurt, and to tell others when they were not feeling well.²⁵ It has also been suggested that there might be a higher incidence of illness such as dysmenorrhoea in adolescent girls.²³

(ii) *Mother's education*—Previous research has shown that the predicted number of days that a child with a chronic disease was away from school was found to decrease as the education of the primary caregiver increased.⁷ Our study also showed the level of mother's education to be an important factor. The reasons for this association are not clear but several might be suggested. Mothers who left school at the earliest opportunity and perhaps disliked school themselves might have a negative attitude to school and be unwilling to 'force' their child into it. It is also suggested that mothers with less education might have less skill and knowledge to overcome some of the problems associated with the disease.⁷ There is also the likelihood that these mothers are less affluent. Hardship and poverty have been shown to be linked with high absence rates in children with chronic illness,⁹ and in general. These families are less likely to own a car, and transport to school of a child with physical problems could then present difficulties, especially if the mother was unfamiliar with the procedures needed to get transport provided.

The mother's attitude can be important. For example, mean absentee rates in a sample of children with asthma were related to the mothers' view of the severity of the asthma: mild (6.9% absence), moderate (7.9%), and severe (13.9%).¹⁰ There is a real, understandable risk of overprotectiveness by parents¹⁷ and of family patterns of keeping children off school for minor ailments,¹⁶ both of which can lead to more absence than is necessary. The latter was also shown in respect to young cardiac patients.¹³ School phobia, based on unconscious conflicts and fantasies, can take many guises and can fool mothers.²⁶ It can be prevented, but keeping the child off school is not the answer.

(c) Effects

Chronic illness as related to school has been shown to include an increased risk of social isolation, trouble at school, poor attitude to school work, truancy, and school absences.²⁷ Further negative effects have been shown in a study of asthma patients¹¹ and other chronic disease patients,⁶ 17% and 30% of whom respectively had to repeat a school year. Falling behind and repeating a year was one of the greatest fears and worries expressed by children who had been treated for cancers.²²

Evidence is totally conflicting as to whether or not excessive absence leads to poorer achievement scores. Some studies showed a link between poor attendance and poor scores, others have failed to do so. There is, however, no doubt that many young cancer

patients^{15 18 19 28} and chronic disease patients^{6 11} do experience problems with progress in school subjects.

On the positive side, even as long ago as 1975, a study in the USA of a group of people who had been treated for childhood cancers at least 10 years earlier reported that they had achieved much academically.²⁹ If this could be done by patients treated over 25 years ago, how much more should be expected of present day child cancer patients.

School is important. It is all too easy for parents and teachers to think in the short term, seeing only the immediacy of the disease. Teachers tend to assume that when a child with a known serious illness is absent from school, the absence will be associated with that illness and they also tend to be more lenient to child cancer patients.¹⁹ They therefore accept the absence without question. In fact, the absences not caused by treatment are by no means always related to the illness. A study of asthmatic children's attendance showed that their absences were rarely related to the asthma, but they were absent for the same reasons as those of children in general, as were some in our study.

Children who suffer serious disease have a future, whether it be short or long. Their careers are important to them, and many have already made their career choice. As one 10 year old girl said, 'If I can't have children, my career is more important to me than to most people. I must leave something good for the world'.

A great deal is already being done,³⁰ but changing prognoses bring changing needs.

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Treatment of cardiac arrhythmias using radiofrequency current

As we all know, the cardiologists are getting cleverer and cleverer with their catheter techniques. Two articles, from workers in Oklahoma and Michigan, published side by side in the 6 June issue of the *New England Journal of Medicine* report high success rates using radiofrequency current to ablate accessory conduction pathways in the treatment of the Wolff-Parkinson-White syndrome and of recurrent paroxysmal supraventricular tachycardias (Warren M Jackman and colleagues and Hugh Calkins and colleagues, 1991;324:1605-11 and 1612-18).

Initial attempts at percutaneous catheter ablation used high energy direct current shocks with a high success rate but serious morbidity in a few patients. The use of radiofrequency currents (550-750 kHz) is associated with much less risk. In the first of these two studies the youngest patient was 6 and five were under 9 years. The youngest in the second study was 15. Elimination of accessory pathway conduction was achieved in 99% (164/166) of patients in Oklahoma and 92% (94/102) of patients in Michigan. In the two studies combined, five of 268 suffered complications—atrioventricular block in two and coronary occlusion, pericarditis, and cardiac tamponade each in a single case.

The technique does not supercede drug treatment but it is recommended for patients with severe symptoms who have not responded to the drugs.

ARCHIVIST

PS. Everybody's doing it. See Karl-Heinz Kuck and colleagues (*Lancet* 1991;337: 1557-61).

Neural tube defects, maternal cohorts, and age: a pointer to aetiology

J P Bound, B J Francis, P W Harvey

Abstract

The effects of maternal year of birth and age on the declining prevalence of neural tube defects after 1972-3 were examined using 403 cases ascertained in a prospective study in the Fylde of Lancashire during 1957-89. Matched case-control data were analysed using conditional logistic regression analysis.

The risk of an anencephalic baby was significantly greater for older mothers, but changes in the maternal age distribution in the population did not appear to be relevant to the recent decline in prevalence. Antenatal diagnosis and termination of pregnancy was the major cause.

Mothers born before 1950 were at significantly greater risk of producing a baby with spina bifida or cranium bifidum. We suggest that abandonment of mercury as a therapeutic agent for infants in the early 1950s is a possible factor in the current decline of these malformations.

This paper examines the relationship between year of maternal birth, maternal age, and the prevalence of neural tube defects in the Fylde of Lancashire, with particular reference to the decline after 1972-3.

Janerich showed by cohort analysis that the absolute risk of anencephaly was more directly related to the mother's year of birth than to that of the affected child.¹ This suggested that environmental aetiological factors act early in the mother's life affecting the risk of anencephalic offspring throughout her reproductive period.

In the Fylde during 1957-76 the prevalence of anencephaly fell suddenly and significantly after 1968.² The prevalence of spina bifida and cranium bifidum also fell, but to a lesser extent. Subsequently, after the early 1970s, both types of neural tube defect declined.

In England and Wales the decline in prevalence of neural tube defects that began in 1972 was not explicable solely by prenatal diagnosis and termination of pregnancy.³ In Liverpool the decline from 1974 was more noticeable for anencephaly than spina bifida.⁴ In Sheffield a dramatic decline in spina bifida births was partly due to antenatal diagnosis and termination, which was even more successful in reducing anencephaly.⁵

We have sought to explain the underlying decline by looking for a maternal age or cohort effect and, if found, a cause.

Methods

Cases of neural tube defect were ascertained as part of a prospective survey, described in detail

previously, of babies with major congenital malformations born in the Fylde to residents there during 1957-81.⁶ Data was collected daily by one paediatrician and a very high rate of necropsies was maintained. Recording of cases was continued until the end of 1989. Terminations of pregnancy for antenatal diagnosis of neural tube defects were ascertained from the local obstetricians' records.

The total numbers of cases, including terminations, were 190 for anencephaly, 181 for spina bifida cystica, and 32 for cranium bifidum cysticum (excluding five early cases where the mother's date of birth was not known). There were 116 282 live births and stillbirths in the 33 years (1957-89).

The separation of the effects of maternal age at birth of child, year of birth of the child (or termination of the pregnancy), and year of birth of the mother cannot be achieved using a standard study design, as the date of birth of the child (BC) is mathematically defined by the date of birth of the mother (BM) and the age of the mother (AM) through the relation $BC = BM + AM$. The statistical problem in separating the (maternal) age, (birth) period, and (maternal) cohort effects has been discussed by many authors.⁷⁻⁸ Plewis makes the point that it is always possible to design a study to estimate any two of these three effects, and gives several study designs.⁹

In this study, we have adopted a matched case-control approach; by controlling for year of birth of the child then the effects of maternal age and maternal year of birth may be separated by suitable statistical techniques. This procedure allows us to seek an explanation for a known temporal effect (the decrease in the rates of anencephaly and of spina bifida and cranium bifidum after the early 1970s).

Controls were obtained from birth records of the consultant obstetric hospital, which served all the Fylde. It was possible, therefore, to match cases born outside the hospital with controls from the same district. A single control was used for each case, taking the first birth of a normal baby for the same year and month which matched for district of residence of the mother and sex of the baby. The date of birth and parity of the control mother was then recorded.

The statistical analysis of matched case-control data using conditional logistic regression analysis is described in Breslow and Day.¹⁰ The statistical package GLIM is well suited to fit such models and Adena and Wilson describe a range of procedures.¹¹⁻¹² We used their procedures, but included the full set of nuisance parameters in the linear model¹³ giving us greater accuracy. Maternal age and

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maternal year of birth were treated as categorical variables.

We adopted a backward elimination procedure for determining a suitable model; firstly by including all risk factors of interest—maternal age, maternal year of birth, and parity—in the initial model and then at each stage excluding the most unimportant variable, using the deviance (likelihood ratio statistic) as a criterion for comparing nested models.¹³ The procedure terminated when all remaining risk factors were significant. In this way the competing effects of maternal age and maternal year of birth could be assessed.

Separate analyses were carried out for anencephaly and for spina bifida and cranium bifidum. For each analysis, we provide a table of relative risk factors for the final model with 95% confidence intervals. For maternal age, the risks are relative to the youngest age group, and for maternal year of birth, the risks are relative to the earliest maternal birth cohort.

Results

After 1972 anencephalic births in the Fylde declined to zero (tables 1 and 2). Much of this fall was due to antenatal diagnosis of anencephaly with termination of pregnancy. Births of babies with spina bifida and cranium bifidum also declined after 1973 but the fall was less than for anencephaly. However there were fewer terminations for spina bifida and cranium bifidum so that the underlying decline in prevalence was greater than for anencephaly.

ANENCEPHALY

Parity (changes in deviance=0.36 on 1 df; p=0.55) followed by maternal year of birth (change in deviance=1.84 on 3 df; p=0.61) were found to be unimportant and were excluded from the logistic regression model. A strong effect of maternal age was observed which could not be excluded from the model (change in deviance=17.66 on 2 df; p<0.0001).

Table 1 Prevalence of neural tube defects in the Fylde of Lancashire 1957-89

Period	Total births	Anencephaly		Spina bifida and cranium bifidum	
		Births	Prevalence/1000 births	Births	Prevalence/1000 births
1957-61	18321	59	3.2	57	3.1
1962-66	20827	53	2.5	58	2.8
1967-71	19132	24	1.3	40	2.1
1972-76	15281	20	1.3	31	2.0
1977-81	14888	9	0.6	11	0.7
1982-86	16488	2	0.1	7	0.4
1987-89	11345	0	0.0	3	0.3

Table 2 Prevalence from 1977 including terminations of pregnancy for antenatal diagnosis of neural tube defects

Period	Total births	Anencephaly		Spina bifida and cranium bifidum	
		Births	Prevalence/1000 births	Births	Prevalence/1000 births
1977-81	14888	13	0.9	11	0.7
1982-86	16488	12	0.7	13	0.8
1987-89	11345	9	0.8	8	0.7

Table 3 Maternal age and relative risk for anencephaly

	Relative risk	95% Confidence interval
Maternal age:		
25-29 v <25	1.921	1.134 to 3.251
≥30 v <25	2.910	1.704 to 4.967

Table 4 Maternal year of birth and relative risk for spina bifida and cranium bifidum

	Relative risk	95% Confidence interval
Maternal year of birth:		
1940-1949 v pre-1940	0.9336	0.548 to 1.590
1950-1959 v pre-1940	0.2574	0.085 to 0.783
Post 1959 v pre-1940	0.2845	0.068 to 1.191

The relative risk for mothers over 25 is nearly double that for younger mothers (table 3), and the relative risk increases still further for mothers over 30, being nearly treble that of younger mothers.

SPINA BIFIDA AND CRANIUM BIFIDUM

Parity was again the least important variable (change in deviance=0.04 on 1 df; p=0.84) but maternal age (change in deviance=1.15 on 2 df; p=0.56) was also found to be unimportant and was excluded from the model, leaving maternal year of birth as the only important factor (change in deviance=7.90 on 3 df; p<0.05). Replacing the maternal year of birth factor by a linear trend for maternal year of birth produced a significant change of deviance of 5.99 on 2 df (p=0.05) and the linear trend was no longer significant (change in deviance=1.91 on 1 df; p=0.17).

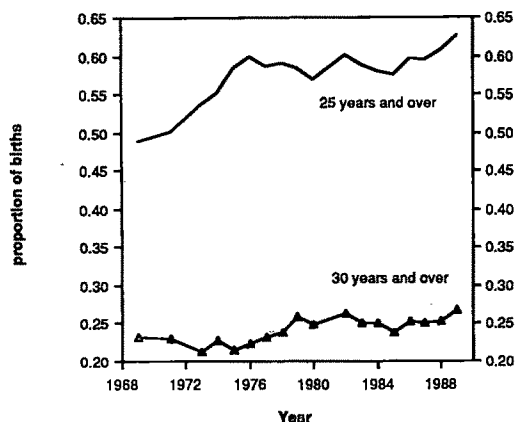
It can be seen from table 4 that maternal year of birth is a significant risk factor. The relative risk is close to one until 1950, then declines substantially. For mothers born before 1950, the risk of spina bifida or cranium bifidum is more than treble that for mothers born after 1950.

Discussion

The sudden significant fall in the prevalence of anencephaly in the Fylde after 1968 was not seen in north west England or nationally. It was associated with increasing hardness of the summer water in a supply which was confined to the Fylde.² The prevalence of spina bifida and cranium bifidum showed a small fall that was not significant.

After 1972-3 the prevalence of both anencephaly and spina bifida and cranium bifidum in the Fylde declined again, reflecting the trend in England and Wales.³ Further, antenatal diagnosis of a neural tube defect with termination of the pregnancy, which was more successful in reducing anencephaly, could explain only part of the decline in prevalence, especially of spina bifida as was found in Sheffield.⁵ Therefore our trends since 1972 are in accord with those found elsewhere and the results of the cohort studies should have general relevance.

The idea that environmental factors acting during the mother's early life could predispose her to produce babies with neural tube defects



Proportion of births in Fylde for two maternal age groups. Proportions based on hospital births up to 1980 and on all births from 1980.

later is not new. It has been suggested that non-specific interference with early growth and development may affect the reproductive and/or endocrine systems and contribute to the later production of neural tube defects.¹⁴ The interference could be short or long lived and produced by many conditions, such as nutritional deficiencies, severe illness, or socio-cultural factors. Recently, a related idea has been proposed that environmental programming in fetal and infant life affects adult degenerative disease.¹⁵

ANENCEPHALY

We have found that the mother's year of birth did not affect her risk of having a baby with anencephaly. Her age did, the risk increasing in older mothers. However, apart from a slight dip in the proportion of mothers aged 30 years or more between 1971 and 1977, seen both in the Fylde (figure) and nationally, the proportion of older mothers increased up to 1989. Therefore the declining prevalence of anencephaly was unlikely to be due to change in maternal age distribution.

SPINA BIFIDA AND CRANIUM BIFIDUM

Maternal year of birth was an important risk factor. The evidence is that the decline in risk was sudden rather than gradual, with mothers born after 1949 significantly less likely to have an affected baby. In other words, fewer mothers could be regarded as preconditioned to have a baby with these anomalies. This is chronologically compatible with the fewer recorded births of affected babies after 1973 and suggests that, apart from termination, the underlying cause of the decline is to be sought in events in the early 1950s.

Janerich suggested that the 1918–9 influenza pandemic may have been a preconditioning event for the epidemic of neural tube defects which peaked in 1929–32.¹⁶ However it is not possible to relate the current decline in spina bifida to the pattern of influenzal infections. For example, if the pandemics of 1957 and 1969 were preconditioning events, an increased

prevalence of spina bifida would have been expected at a time when, in fact, it was in a prolonged decline.

Dietary deficiencies have also been suggested for preconditioning events. The most noticeable general improvement in nutrition occurred in 1940 with rationing and the provision of welfare foods for mothers and children.¹⁷ This led to an immediate steep fall in perinatal mortality and improved growth of children, but we find little change in the risk to future mothers of a baby with spina bifida. The significant change occurred some 10 years later and we are unaware of any further relevant improvement in diet then.

Searching for other possible preconditioning events we noted that mercury was largely abandoned in the treatment of infants in the early 1950s. From 1948 warnings were given that the metal could cause pink disease in susceptible infants.^{18 19} Mercury nephrosis was also described.²⁰ Apart from doctors' prescriptions of grey powder (mercury with chalk) or calomel for constipation and other symptoms in infants, calomel was a constituent of many proprietary teething powders which were widely used. For example, it was found that approximately 40% of the infant population of Manchester and Salford, and also of Warwickshire, received them.¹⁹ Absorption of the metal could also occur from the use of mercurial ointments for treating napkin rashes. By 1955 a decline in pink disease and less mercury ingestion in infants was reported from Sheffield.²¹ It became clear that mercury had caused a prolonged, serious, sometimes fatal illness in some infants. In addition, abortive cases had been common.²² Anorexia was a prominent feature and mercury could have exerted its effect on subsequent reproduction through a period of malnutrition. Additionally, mercurial toxicity could have been specific as it has been reported to affect the germ cells of mammals.²³

We suggest that administration of mercury was a possible preconditioning event for subsequent spina bifida or cranium bifidum and should be borne in mind when studying their aetiology, although it may now be difficult to obtain additional evidence to support the chronological findings.

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Tuberculous hydrocephalus

As I was saying (1991;66:151), hydrocephalus occurs in a large majority of children with severe tuberculous meningitis. The best way of treating this hydrocephalus is uncertain and a report from South Africa compares several possible treatments (J Schoeman and colleagues, *Developmental Medicine and Child Neurology* 1991;33: 396-405). The study included 81 children aged 5 months to 8 years with severe tuberculous meningitis of MRC stages II and III at admission. (Stage I, early, mainly non-specific symptoms, little or no clinical sign of meningitis, no pareses, general condition good, fully conscious. Stage II, intermediate between I and III. Stage III advanced, extremely ill, deeply stuporose or comatose or with gross pareses.¹) All the children received antituberculous treatment with four drugs; isoniazid, rifampicin, ethionamide, and pyrazinamide. Communicating hydrocephalus was present in 63 and non-communicating in 18. Those with non-communicating hydrocephalus were all treated early with a ventriculoperitoneal shunt. Those with communicating hydrocephalus were allocated randomly to one of four treatment groups: group A, no extra treatment (n=19), group B, weekly intrathecal hyaluronidase (n=19), group C, oral acetazolamide and frusemide (n=19), and group D, shunt surgery. Group D was discontinued after six patients had been operated upon because the authors considered the results of medical treatment to be 'encouraging'.

The lumbar cerebrospinal fluid pressure fell to normal over the first month in 41% of surviving patients in group A, 71% in group B, and 78% in group C, but mortality and morbidity were high in all groups and unaffected by the type of treatment. The overall mortality was 8% for stage II disease and 30% for stage III. Of the survivors of stage III disease 66% were severely mentally impaired (IQ<50), 27% were moderately mentally impaired (IQ 50-85), and 71% had a quadriplegia or a hemiplegia. Of stage II disease survivors 14% were severely mentally impaired, 69% moderately mentally impaired, and 26% had quadriplegia or hemiplegia.

The severity of disease at presentation is the most important factor determining outcome. This work has not shown that treatment of the hydrocephalus does anything to help these children. Intrathecal hyaluronidase did not seem to have harmful effects but acetazolamide and frusemide produced dehydration in three patients possibly associated with sagittal sinus thrombosis in one. Of the 24 children who had a ventriculoperitoneal shunt procedure five developed shunt dysfunction. Four of these had an infected shunt and they all died. These authors give no compelling reason for treating communicating hydrocephalus in tuberculous meningitis, although they advocate treatment with acetazolamide and frusemide. For non-communicating hydrocephalus they recommend early shunt surgery but the data they present do not permit an evaluation of that recommendation.

ARCHIVIST

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Retropharyngeal abscess

Mark Coulthard, David Isaacs

Abstract

Of 31 children with retropharyngeal abscess treated at this hospital between 1954 and 1990, 17 (55%) were 12 months old or less and 10 (32%) less than 6 months. Three of these 10 children were neonates, only one of whom had a predisposing congenital lesion. Fourteen children (45%) had a preceding upper respiratory illness and four (13%) had a prior history of pharyngeal trauma or ingestion of a foreign body.

In children less than 1 year old the clinical presentation was usually classical with fever, neck swelling, stridor, and pharyngeal swelling. Significantly fewer children over 1 year old had neck swelling and no child over 3 years old had stridor. A lateral radiograph of the neck, when performed, had a sensitivity of 88% in diagnosis.

Bacteria isolated included pure growths of *Staphylococcus aureus* (25%), *klebsiella* species (13%), group A streptococcus (8%), and a mixture of Gram negative and anaerobic organisms (38%). There were two deaths. In six cases (24%) the abscess recurred necessitating further surgical drainage.

Deep infections of the head and the neck have been recognised since the time of the Greek physician Galen, who is reported to have described a case of retropharyngeal abscess.¹

Retropharyngeal abscess is an uncommon infection of the deep neck spaces but has its highest incidence in the paediatric population. Retropharyngeal abscesses can result in acute upper airway obstruction, septicaemia, mediastinitis, aspiration pneumonia, empyema, and serious vascular complications, including thrombosis of the internal jugular vein and erosion of the internal carotid artery.²⁻⁸

Methods

A review was undertaken of the charts of all children in the Children's Hospital, Camperdown between 1954 and 1990 who had a discharge diagnosis of retropharyngeal abscess. Most cases were confirmed operatively or after spontaneous rupture, but some cases were defined as having retropharyngeal abscess on the basis of a characteristic clinical picture and widening of the retropharyngeal space on lateral neck radiograph to at least twice the diameter of the cervical vertebrae. We reviewed the age of patients, clinical presentation including predisposing factors such as trauma or upper respiratory infection, the organisms isolated,

and the outcome. Microbiology results are reported for pus obtained by needle aspirate or surgical excision only. Conventional bacteriological techniques were used for isolation and identification of organisms. Statistical analysis was by χ^2 or Fisher's exact test for absolute numbers and Student's *t* test for means.

Results

A total of 31 children were treated for retropharyngeal abscess between 1954 and 1990; there were 17 boys (55%) and 14 girls (45%). The age distribution is shown in fig 1. There were 17 cases (55%) 12 months old or less and 10 cases less than 6 months (32%). Three cases (10%) presented in the neonatal period. One newborn suffered recurrent abscess formation until a pyriform fossa sinus was demonstrated and excised at age 6 months. The other two neonatal cases had no known predisposing factors such as intubation or laryngoscopy. The youngest child was age 6 days on admission and the oldest was 12.2 years.

A preceding illness including upper respiratory infection, tonsillitis, isolated cervical lymphadenitis, and herpetic gingivostomatitis in one case, was recorded in eight of 17 (47%) children under 1 year and six of 14 (43%) children over 1 year. One child had been bitten in the neck by a dog. Four children (13%) had a history of trauma to the pharynx or ingestion of a foreign body. These four cases included: (i) swallowing a safety pin which was removed two weeks before the retropharyngeal abscess developed, (ii) falling over with a pencil in the mouth and traumatising the posterior pharynx, (iii) swallowing two drawing pins, one of which was removed at drainage of the abscess, and (iv) swallowing a piece of plastic three days

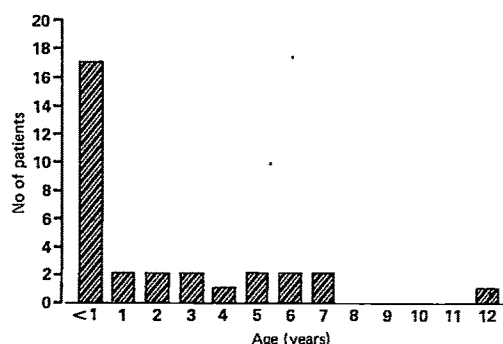


Figure 1 Age distribution of patients with retropharyngeal abscess from the Children's Hospital, Camperdown, 1954-90.

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previously. No case followed instrumentation of the oesophagus or upper airway. Therefore, in the remaining 13 cases (42%) no prodrome or precipitating factor was reported.

The presenting symptoms and signs are reviewed in table 1. In those children of 1 year or less, the presenting clinical picture was usually 'classical' with fever, stridor and neck swelling, and a pharyngeal mass was often seen. The three neonates, however, were afebrile. Children over 1 year were significantly less likely to have swelling of the neck, and stridor was not present in any child over 3 years old. The difference was not due to prior antibiotic treatment, which was equally common in children under and over a year old (table 1).

The median duration of symptoms was four days both for children under and those over 1 year old, while the mean (SD) duration of symptoms was 5.29 (4.75) days and 5.71 (4.61) days respectively ($t=0.25$, $p>0.1$).

A lateral radiograph of the neck, to display the soft tissues, was performed in 24 cases (77%) and was diagnostic in 21 (88%), showing a widened prevertebral space (fig 2). A computed tomogram of the neck was performed in only one case. Most children had a chest radiograph performed and all of these were initially abnormal.

Treatment was most often the institution of antibiotics followed by surgical incision and drainage of the abscess. Spontaneous rupture of the abscess occurred in three cases (10%); this

was followed by antibiotic treatment. In five cases (16%) antibiotics alone was prescribed.

An analysis of the organisms isolated from 24 cases of retropharyngeal abscess is shown in table 2. Results are not available in those cases where the abscess ruptured spontaneously or where antibiotic treatment alone was undertaken. In the 24 cases (77%) in which culture results were available, there were six pure isolates of *Staphylococcus aureus* (25%), three pure isolates of klebsiella species (13%), two pure isolates of group A streptococcus (8%), and nine isolates (38%) included a mixture of Gram negative and anaerobic organisms. Of the four cases which followed trauma to the pharynx, the results were available in three. In these three cases there was a pure growth of klebsiella, a mixture of *Escherichia coli* with *Streptococcus faecalis* and a mixture of *E coli* with *Haemophilus influenzae* respectively.

There were two deaths, both before 1965: a 3 week old baby presented with paraplegia caused by a fracture dislocation of the atlas and axis secondary to retropharyngeal abscess; and the diagnosis was not made until necropsy in a 3 month old baby. The abscess recurred in six cases necessitating repeat surgical drainage. Tracheostomy was performed on three children before surgical drainage. Six children, all less than 1 year old, required intubation either pre-operatively or postoperatively.

Table 1 Presenting features of children with retropharyngeal abscess by age from the Children's Hospital, Camperdown, 1954-90. Results are number (%)

Presenting features	≤1 year (n=17)	>1 year (n=14)	p Value
Fever	12 (71)	8 (57)	NS
Stridor/respiratory difficulty	12 (71)	6 (43)	NS
Neck swelling	12 (71)	2 (14)	<0.005
Pharyngeal mass	9 (53)	4 (29)	NS
Dysphagia/feeding problems	6 (35)	4 (29)	NS
Cervical lymphadenopathy	5 (29)	5 (36)	NS
Torticollis	3 (18)	1 (7)	NS
Sore throat	—	4 (29)	—
Neck pain	—	4 (29)	—
Prior antibiotic treatment	6 (35)	7 (50)	NS

ANATOMY

The anatomy of the deep neck spaces and associated fascial planes^{1-3 6 7} is helpful in understanding retropharyngeal abscess (fig 3).

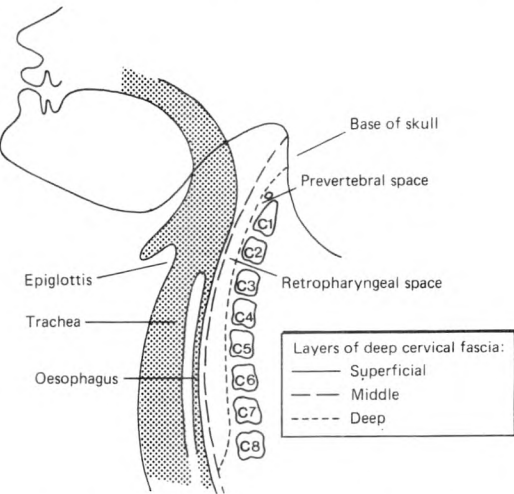


Figure 3 Mid-sagittal section of the head and neck illustrating deep neck spaces.

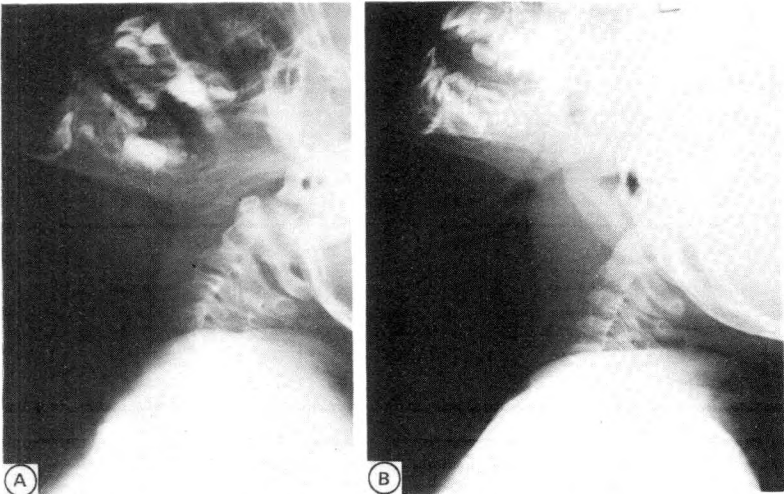


Figure 2 Lateral neck radiograph. (A) Normal film. (B) Increase in soft tissue shadow between cervical vertebrae and posterior wall of air filled pharynx indicating the presence of a retropharyngeal abscess.

Table 2 Organisms isolated from 24 cases of retropharyngeal abscess from the Children's Hospital, Camperdown, 1954-90

Organisms isolated	No (%)
Mixed Gram negative and anaerobes	9 (37.5)
<i>Staphylococcus aureus</i> alone	6 (25)
Klebsiella species alone	3 (12.5)
Group A streptococcus alone	2 (8)
<i>Staphylococcus aureus</i> and group A streptococcus	1 (4)
<i>Staphylococcus aureus</i> and klebsiella species	1 (4)
Microaerophilic streptococcus	1 (4)

The retropharyngeal space lies between the buccopharyngeal fascia, which is the middle layer of the deep cervical fascia, and the prevertebral fascia, which is the deep layer. It extends from the base of the skull to the level of T1 in the superior mediastinum where the two layers fuse. Infection can spread directly into the anterior and posterior mediastinum anteriorly, so that mediastinitis is a rare complication of retropharyngeal abscess.

The retropharyngeal space contains two paramedial chains of lymph nodes which drain the nose, paranasal sinuses, nasopharynx, and adenoids. These lymph nodes are prominent in young children but involute in late childhood.¹⁻⁴ Infection of the lymph nodes can thus result from lymphatic spread from these adjacent structures and suppuration may result in abscess formation.

Discussion

Retropharyngeal abscesses are most commonly reported in children under the age of 3 years. Our population covered a wide range of ages but retropharyngeal abscess was most common in children under 12 months of age, and nearly a third were under 6 months old. Three cases presented in the neonatal period. Other studies have reported a similar age distribution at presentation,⁷⁻⁹ although one study reported no cases over the age of 6 years¹⁰ and neonatal cases are generally rare. We found a slight male preponderance (55%), which has been reported in other studies.^{1 7-10}

Retropharyngeal lymphadenitis may result from spread along the lymphatics from sites of infection in the ear, nose, or throat and may subsequently form an abscess. A history of a preceding upper respiratory illness was recorded for nearly half our patients and was equally common in infants and older children. Direct implantation of pathogens can follow the impaction of a foreign body into the oropharynx.^{1-4 9} However, we found that a preceding history of trauma was uncommon.

The clinical presentation is often insidious and the diagnosis may be difficult. In our study, children under 1 year of age presented 'classically' with fever, neck swelling, stridor or respiratory distress, a pharyngeal mass, cervical lymphadenopathy, and head tilt. Older children were less likely to have neck swelling and no child over 3 years had stridor. They were most likely to have specific complaints such as neck pain or stiffness and sore throat. It is possible that neck swelling is more likely to occur in younger children because of less well defined fascial planes. We did not find that older children were more likely to have delay in diagnosis.

We found that a lateral radiograph of the neck when performed had an 88% sensitivity in diagnosing retropharyngeal abscess, other cases being diagnosed clinically on the basis of pharyngeal swelling. The diagnostic radiological feature is an increase in the width of the retropharyngeal space, which is measured from the posterior wall of the pharynx, as defined by the air column within, and the anterior border

of the second cervical vertebra.⁶⁻¹⁰ A widened retropharyngeal space is usually defined as being more than twice the diameter of the cervical vertebrae. However, this appearance can be mimicked by flexing the neck, so that lateral radiographs should be taken with the neck in extension. Additional helpful radiological features include gas or a visible fluid level within an abscess cavity, the presence of a foreign body, and prevertebral muscle spasm resulting in loss of the normal curve of the cervical spine. Widening of the retropharyngeal space could be due to abscess or to inflammatory oedema without a formed abscess. A computed tomogram may differentiate between cellulitis and true abscess formation and identify abscess extension into other fascial planes.¹¹ Ultrasound examination might also distinguish these entities, but has not yet been adequately evaluated. A chest radiograph will assess the presence of empyema or mediastinitis.^{4 12}

In five of our cases treatment comprised antibiotic therapy alone and all of these cases recovered uneventfully. Surprisingly, these children were treated towards the beginning of the series when one might expect less reliance to be placed on antibiotics alone. All cases in the past 10 years have been treated with both surgical drainage and antibiotics. This finding contrasts with that of another recent study in which their surgical rate is falling slowly and most recently was 70%.⁷

We found that mixed infections with Gram negative bacilli and anaerobes were the most common isolates, although *S aureus* was the most common single organism, and three children had pure isolates of klebsiella species. Other studies have emphasised the role of mixed aerobic and anaerobic infections.^{13 14} On the basis of our organisms, we would recommend a penicillinase resistant penicillin combined with a third generation cephalosporin and metronidazole or alternatively clindamycin and an aminoglycoside. We still feel, however, that surgical drainage is the mainstay of treatment because of the danger of aspiration and of airway obstruction.

Six (24%) of our cases of retropharyngeal abscess recurred and further surgical drainage was required. This figure is high compared with another report.⁷ Two of the four children who sustained trauma to the pharynx suffered a recurrence. There were two deaths early in this series, one from a rare but recognised complication of retropharyngeal abscess and the other when the diagnosis was not made until necropsy. This emphasises the importance of recognising this rare, life threatening condition.

We wish to thank the surgeons of the ear, nose, and throat department at the Children's Hospital, Camperdown for the opportunity to report their patients. We thank Carol Dunn from medical illustration for the line drawing.

The three neonatal cases are to be reported in detail elsewhere.

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Acupuncture and vomiting

An interesting review article in the *Postgraduate Medical Journal* (J W Dundee and C McMillan, 1991;67:417-22) summarises the evidence for acupuncture as an antiemetic for postoperative vomiting, morning sickness, vomiting induced by cancer chemotherapy, and travel sickness. Apparently several acupuncture sites are suggested for control of vomiting but the one most accessible and most studied is known as Neiguan or G Jo point No 10 and is situated 'the width of 2 thumbs above the distal crease on the inner wrist in line with the middle finger'. Stimulation at the approved site may be by acupuncture with either manual rotation or electrical stimulation of the needle or by non-invasive methods such as transcutaneous electrical stimulation via surface electrodes or pressure applied either manually or by using an elastic band with a plastic stud (Choy bands, or Sea Bands). The latter are commercially available and have been hailed in the American press as a cure for sea sickness but scientific investigation of their effectiveness has produced disappointing results.

Dundee and McMillan conclude that acupuncture is effective in preventing postoperative vomiting and vomiting after cancer chemotherapy when used as an addition to standard drug treatment. In the latter case, acupuncture is better than transcutaneous electrical stimulation but the effect may be prolonged by frequent application of manual pressure.

No studies in children are mentioned on the article but its simplicity and safety make it an attractive idea. A study in migraine is said to have shown a reduction in sickness but not in pain.¹ Perhaps it would be worth a trial in severe cyclical vomiting.

How does it work? Who knows? We've all heard the endomorphin theory but there is debate about whether that is the explanation of acupuncture induced analgesia and, in any case, it doesn't seem to explain the antiemetic effect.

' but this is wondrous strange!'

'And therefore as a stranger give it welcome
There are more things in heaven and earth, Horatio,
Than are dreamt of in your philosophy'.

But the peculiarity of our philosophy, sweet prince, is that having dreamt we must experiment. The dream comes first though; that's the hypothetico-deductive method, folks (See Peter Medawar. *Philo's Republic*. Oxford: Oxford University Press, 1984:73-135) and *that's* the difference between medicine and magic.

ARCHIVIST

¹ Lenhard L, Waite PME. Acupuncture in the prophylactic treatment of migraine headaches: pilot study. *NZ Med J* 1983;96:663-6.

Prostacyclin concentrations in haemolytic uraemic syndrome after acute shigellosis in children

A N Alam, N M Abdal, M A Wahed, B Rao, C A Kawser, M Hoque, M M Rahaman

Abstract

The role of prostacyclin in the pathogenesis of haemolytic uraemic syndrome was evaluated in 11 children with acute shigellosis. Plasma concentrations of 6-keto prostaglandin, $F_{1\alpha}$, a stable metabolite of prostacyclin, were measured by radioimmunoassay during acute illness, early convalescence, and after clinical recovery. Its concentration was low during acute illness in each patient, returning to normal concentrations or above at the time of the last sample. These results suggest that plasma prostacyclin may be involved in the development of the syndrome.

Haemolytic uraemic syndrome (HUS) is one of the most important causes of acute renal failure in childhood in some regions of the world.¹ The association of severe shigellosis with HUS has been well established,^{2,3} but the pathogenesis of HUS remains unclear. Deficiency of prostacyclin has been implicated in the pathogenesis of the syndrome.⁴⁻¹⁰ Prostacyclin infusion has also been used in the treatment of HUS either with improvement¹¹ or equivocal results.¹² On the other hand, a recent study in five children with HUS showed that plasma 6-keto prostaglandin $F_{1\alpha}$ ($PGF_{1\alpha}$), the sole stable degradation product of prostacyclin (PGI_2), was raised.¹³ The present study was aimed at evaluating the concentrations of prostacyclin by measuring $PGF_{1\alpha}$ after severe shigellosis in children during the acute and convalescent stages as well as after clinical recovery.

Patients and methods

SELECTION OF PATIENTS

The study was designed to allow estimation of $PGF_{1\alpha}$ on each patient during the three different stages of the illness: on development of HUS (acute stage), during early convalescence (4-5 days after diagnosis of HUS), and on recovery (>15 days after diagnosis, or when serum creatinine concentrations return to normal). This was considered appropriate as each patient acted as his or her own control after recovery. To determine the normal value of prostacyclin, it was measured in 18 apparently healthy volunteers.

One hundred children between 1 and 10 years of age (median age 6 years) with severe shigellosis (characterised by passage of frank blood in the stool with fever, abdominal pain, and signs of toxæmia) with a mean duration of nine days were screened between April 1985 and March 1986 for the development of HUS as indicated

by a fall in packed cell volume, thrombocytopenia, and renal failure. Of these, 11 patients were studied prospectively when they developed leukaemoid reaction (white cell counts of $>50 \times 10^9/l$), clinical evidence of haemolysis, and oliguria (urinary output of less than 10 ml/kg/day) despite adequate hydration. Development of microangiopathy was indicated by a sudden drop in the packed cell volume (>10% drop within the first week of hospitalisation and presence of more than 2% fragmented red blood cells on peripheral blood smears). Patients with septicaemia and other systemic illnesses were excluded from the study. The study had the approval of the ethics committee of the centre and an informed consent was obtained from the parent or legal guardian before any patient was included in the study.

A finger prick blood sample for a complete blood count and peripheral smear was obtained on admission. Venous blood was collected without stasis for assaying prostacyclin by radioimmunoassay and for coagulation measurements, such as partial thromboplastin time, thrombin time, and prothrombin time using Boehringer coagulation assay kits (Boehringer Mannheim). Blood was also collected for culture, measurement of haptoglobin, and determination of serum protein, electrolyte, and creatinine concentrations. Rectal swab and stool were cultured on admission and the next day on MacConkey's agar and on salmonella-shigella agar for isolation of shigella.

Blood was taken from patients during the acute stage of the illness after hydration, during convalescence, and on recovery. On each occasion 4 ml was collected using an ice cold syringe and was transferred into two tubes containing EDTA (0.7 mg/ml plasma). One tube was centrifuged at 1500 g for 15 minutes at 0°C to obtain platelet-poor plasma and the other tube was centrifuged at 150 g to collect platelet-rich plasma. Both samples were then stored at -20°C for subsequent determination of prostacyclin stimulating activity in the plasma samples.

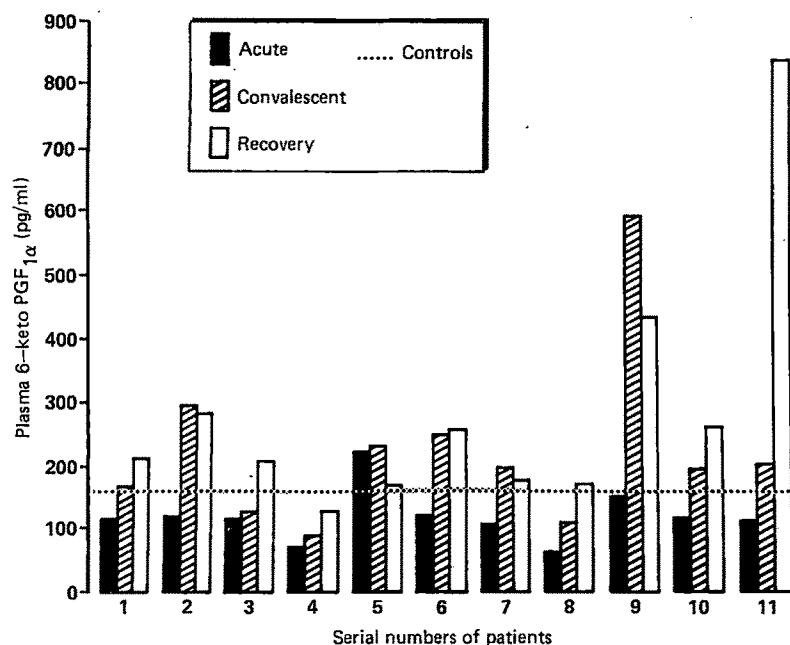
PGI_2 production was measured by the method of Moncada *et al.*¹⁴ This consisted of cutting fresh rabbit aorta into fine rings, kept in tris buffer (0.05 M pH 7.5) on ice for not more than two hours. The rings were then incubated in tris buffer at 22°C for five minutes and washed in ice cold buffer. This step was repeated five times to remove the basal prostacyclin activity. Then, 75 µl of platelet-poor plasma in 200 ml of buffer were incubated with 40 to 60 mg of the clear vascular tissue at 37°C for 15 minutes. At the end of the incubation,

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The plasma concentrations of PGF_{1α} for the 11 patients measured during the acute stage of illness, during convalescence, and on recovery, compared with concentrations from healthy controls.

indomethacin (10 µg/ml) was added to stop further formation of prostacyclin. After removing the vascular tissue the incubants were then stored at -20°C.

6-keto PGF_{1α}, the stable non-enzymatic degradation product of prostacyclin (PGF_{2α}), was then measured in the incubation mixtures by using a radioimmunoassay kit (New England Nuclear (NEN)). Antibody against 6-keto PGF_{1α}, supplied by NEN, has a cross reactivity with PGE₂. A pilot experiment was therefore done to rule out the contribution of PGE₂

Table 1 Clinical characteristics of patients with HUS as studied serially

Case No	Age (years)	Sex	Duration (days)		Bacteriological diagnosis
			Dysentery*	Oliguria/anuria	
1	3	F	12	3	<i>S. dysenteriae</i> type 1
2	6	M	11	5	<i>S. dysenteriae</i> type 1
3	4	M	14	3	<i>S. flexneri</i>
4	3-5	M	7	3	<i>S. dysenteriae</i> type 1
5	5	M	7	7	<i>S. dysenteriae</i> type 1
6	6	M	9	2	<i>S. flexneri</i>
7	10	M	8	2	<i>S. dysenteriae</i> type 1
8	5	M	7	2	<i>S. dysenteriae</i> type 1
9	10	F	8	2	<i>S. dysenteriae</i> type 1
10	9	M	12	7	<i>S. dysenteriae</i> type 1
11	10	M	9	2	<i>S. dysenteriae</i> type 1

*Bloody mucoid stool with accompanying abdominal pain, tenesmus, and fever.

activity in the radioimmunoassay of the incubation mixture.

6-keto PGF_{1α} concentrations were measured on three occasions in 11 children who had developed HUS after shigellosis—during acute illness, during early convalescence, and on clinical recovery.

Plasma haptoglobin was estimated by haemoglobin binding and gel filtration in seven of the 11 patients during the acute stage of the illness and after clinical recovery.

Antibiotic treatment, fresh blood transfusion, and early institution of peritoneal dialysis, as indicated by raised serum creatinine concentrations, were the standard regimen followed for our patients with HUS.

STATISTICAL ANALYSIS

Student's *t* test was used to measure the difference of the means between controls and patients at the acute stage.

Results

Table 1 shows the clinical characteristics of 11 patients recruited for the study. All patients yielded shigella (*Shigella dysenteriae* 1 in nine and *Shigella flexneri* in two). All patients in this study group made complete recovery except one (case 5) who developed chronic renal failure and was lost to follow up after about a year.

Relevant initial laboratory findings in the patients are shown in table 2. All patients had hyponatraemia, hypoalbuminaemia, and raised concentrations of serum creatinine.

Plasma concentration of 6-keto PGF_{1α}, a stable metabolite of prostacyclin, is shown in the figure. At the peak of the acute stage of the illness the mean (SD) value of PGF_{1α} was 135.6 (41.5) pg/ml. The corresponding value in 18 healthy volunteers was 164.1 (29.2) pg/ml. This difference between the normal control and patients at the acute stage was significant (*p*<0.03). The value became higher during the two subsequent sampling periods, returning to normal on recovery. Case 4 did not attain the expected normal concentration of PGF_{1α} even at the recovery stage. The period of observation was relatively shorter in this patient than in other cases.

Results of the coagulation studies are shown in table 3. In seven of nine patients studied, prothrombin time, thrombin time, and partial

Table 2 Initial laboratory findings of study patients with HUS

Case No	Blood			Serum		
	Packed cell volume	Total white cell count (×10 ⁹ /l)	Platelet count (×10 ⁹ /l)	Albumin (g/l)	Sodium (mmol/l)	Creatinine (µmol/l)
1	0.30	67.5	25	30	124	249
2	0.20	70.0	110	32	124	513
3	0.25	59.0	50	28	123	282
4	0.28	50.0	120	30	130	287
5	0.30	60.0	35	32	130	498
6	0.31	61.6	115	25	124	311
7	0.26	55.7	130	34	124	539
8	0.29	60.0	50	26	124	462
9	0.29	69.0	55	30	102	700
10	0.16	84.0	70	32	125	290
11	0.26	65.0	100	26	119	678
Mean	0.26	63.7	80.0	30.3	122.6	428

Table 3 Coagulation abnormalities in patients on development of HUS

Case No	Prothrombin time (s)	Partial thromboplastin time (s)	Thrombin time (s)
1	16 (12)	30 (25)	22 (18)
2	17 (12)	32 (28)	25 (20)
3	22 (15)	25 (28)	22 (18)
4	11 (12)	20 (20)	19 (18)
5	15 (11)	30 (26)	24 (20)
6	15 (11)	25 (20)	24 (18)
7	15 (14)	25 (21)	17 (16)
8	—	—	—
9	—	—	—
10	16 (12)	31 (25)	22 (18)
11	16 (12)	30 (25)	24 (18)

Control values in parenthesis.

Table 4 Serum haptoglobin concentrations (mg/100 ml) in patients with HUS

	Acute (n=7)	Recovery (n=7)	Mean difference
Mean	65.4	212.3	146.9*
SEM	7.6	32.2	30.1

* $p < 0.002$ (paired *t* test).

thromboplastin time were prolonged. Table 4 shows the serum haptoglobin concentrations in seven of the patients who were included in the coagulation studies. Significantly low values were observed in the acute stage of the illness which returned to normal after recovery. The mean (SEM) difference between the recovery and the acute stage was 146.9 (30.1). Although the value in the acute stage was significantly lower ($p < 0.001$) than the healthy controls with a mean (SE) of 183.5 (5.2), the difference between the values from controls and patients on recovery was not significant.

Discussion

The study clearly showed an overall depression of $\text{PGF}_{1\alpha}$ concentrations in patients with HUS during the early phase of the illness which subsequently increased to normal values during early convalescence and on recovery. To our knowledge this is the first reported longitudinal study which measured the concentrations of a prostacyclin metabolite in HUS where the patient acted as his own control. Moreover, the patients in the study were clinically a distinct group in that all had severe shigellosis as the primary illness. HUS after severe dysentery has been reported from the Indian subcontinent since 1975.^{2-3, 15} It seems that during each cycle of a shigellosis epidemic, a fresh crop of patients with HUS are seen.

It is difficult to offer an explanation for these low values of $\text{PGF}_{1\alpha}$ during the early phase of HUS in the absence of other prostaglandin metabolites, such as thromboxane A_2 . Perhaps this low concentration indicates either a high rate of consumption of prostacyclin or poor production. In all cases, after clinical recovery, the prostacyclin concentrations increased significantly, often exceeding those found in the apparently healthy volunteers. Hence, as suggested earlier,^{4, 5} the development of HUS may be a response to the lack of a plasma factor that stimulates prostacyclin activity during the acute stage.

Prostacyclin, a potent vasodilator and inhibitor of platelet aggregation, is produced by the endothelial tissue of the vascular system. It has now been established that endothelial damage is caused by endotoxin, due to Gram negative bacteraemia, a common finding in severe shigellosis, particularly when due to *S dysenteriae* type 1.³ The observed initial lowering of prostacyclin is probably due to its high consumption and/or low production because of the damaged endothelial lining. Subsequent increase is probably due to recovery of the vascular endothelium after clearance of the endotoxin from the circulation.

The changes observed in the coagulation parameters could either be due to the presence of fibrinogen-fibrin degradation products or deficiency of fibrinogen. We could not do fibrinogen-fibrin degradation product measurements in this study. However, mildly abnormal clotting studies in the presence of appreciable thrombocytopenia are compatible with disseminated intravascular coagulation which is commonly associated with HUS. Intravascular haemolysis, as evidenced by significantly decreased values for haptoglobin, was marked only in the acute stage of the illness.

Other laboratory evidence indicates that all these patients made apparently complete recovery from this with the exception of one who developed chronic renal failure.

In this study we could not include patients with acute shigellosis without HUS to act as controls. This would have helped us in understanding whether depression of prostacyclin is a matter of degree or an 'all or none' phenomenon.

HUS is probably not a single disease entity and it is more likely that different pathogenetic mechanisms may underlie different forms of the disease. Levin *et al* found reduced prostacyclin production in children with a sporadic type of HUS, which they thought to be due to the presence of an inhibitory substance.¹⁰ It would be difficult to classify our patients as clearly sporadic or epidemic. All the study children, however, initially had acute shigellosis and most had clinical characteristics of both types.

Our data support the view that in the acute stage of post-shigellosis HUS, lowering of $\text{PGF}_{1\alpha}$ concentrations may have an important role in the pathophysiology of HUS, although endotoxaemia may yet prove to be a precipitating factor in the HUS which develops after shigellosis.

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Lisch nodules

These nodules on the iris were first described by Waardenburg in 1918 but Lisch pointed out their association with von Recklinghausen's neurofibromatosis in 1937. They are small, clear, yellow or brown nodules which project from the surface of the iris and when multiple are thought to be diagnostic of neurofibromatosis. In pathological terms they are melanocytic hamartomas. They can be seen with the naked eye but are best observed and distinguished from naevi on the iris by slit lamp examination. Guidelines for the diagnosis of neurofibromatosis were offered at a consensus conference in 1987.¹ There are two types. Peripheral neurofibromatosis, or von Recklinghausen's disease, is type 1 and type 2 is central neurofibromatosis associated with bilateral acoustic neuromas. Lisch nodules are associated with type 1 disease which may be diagnosed in the presence of two or more of: two or more neurofibromas, one plexiform neurofibroma, axillary or inguinal freckling, optic glioma, two or more Lisch nodules, a typical lesion of bone, or an affected first degree relative.

A recent report from Miami Children's Hospital (Marie-Louise E Lubs and colleagues, *New England Journal of Medicine* 1991; 324:1264-6) examines the significance of Lisch nodules in 167 patients from 120 families with type 1 neurofibromatosis. Under the age of 3 years both Lisch nodules and neurofibromas were uncommon being found in only 5 and 10% of patients respectively. Thereafter the prevalence of both features increased steadily throughout childhood with Lisch nodules being the more common feature at all ages. They were found in 42% of 3 or 4 year olds, about 80% of 9 to 14 year olds, and in all 65 adults over the age of 20 years. Neurofibromas were present in 10% of 3 or 4 year olds, 50% of 9 to 14 year olds, and 95% of adults. Lisch nodules were never the only finding, there were always other signs of the disease, usually café au lait spots. The prevalence of the nodules was not influenced by the clinical severity of the disease, race, sex, family history, or the presence or absence of central nervous system tumours.

The absence of Lisch nodules virtually excludes the presence of the neurofibromatosis gene in an adult. In children with only one of the diagnostic criteria the diagnosis becomes less likely with increasing age in the continued absence of the nodules. The authors calculate that in such circumstances the risk of having the gene is 50% at birth, 15% at 9 to 14 years, and zero over the age of 20 years.

ARCHIVIST

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HIV-I infection in perinatally exposed siblings and twins

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Abstract

In a multicentre study on perinatal HIV-I infection including 1493 children born from 1471 pregnancies to 1415 infected mothers, 22 twin pairs and 56 sibships (115 children) were recorded. The frequency of twin pregnancies was 1.5 (22/1471) and 3.9% (56/1415) seropositive women had more than one at risk pregnancy. In 18 twin pairs with a known infection status nine of the 36 children (25%) were infected. Discordance in infection status was present in only one (5.5%) dizygous pair. A high relative risk of infection (23.1) in a twin was observed when the other was infected. Infection was unrelated to gestational age, mode of delivery, or birth weight. Infection status was defined in 41 sibships (84 children including one first born twin pair and one third born child). When the first born was infected, 11/26 (42.3%) second born children were also infected, whereas this happened in only 2/16 (12.5%) second or third born children when the first born was uninfected. Two out of nine first born (22.2%) and 5/21 (23.8%) second born children prospectively followed up from birth acquired the infection. Results of this study demonstrate that neither twin nor second pregnancies are at increased risk of mother to child HIV-I transmission. Overall data suggest that non-casual factors in mother and/or child influence perinatal infection.

Transmission from the mother to her offspring accounts for most cases of human immunodeficiency virus type I (HIV-I) infection in children.^{1 2} Transmission occurs mostly in utero,³ but intrapartum exposure to maternal blood and vaginal fluid^{4 5} or breast feeding^{2 6} may be additional routes. Results of large studies on efficiency of mother to child transmission have been recently reviewed.²

The risk of vertical transmission of HIV-I in twin or second pregnancies has not yet been defined. Reports on twins⁷⁻⁹ are anecdotal and studies in siblings contain selection bias^{10 11} or are based on very limited series.^{12 13} Studies in twins may provide information on the biological background influencing perinatal transmission⁸ and clinical outcome of infection. In addition, data are needed to counsel HIV-I infected women who wish a second pregnancy.^{10 12} In the present study these issues were addressed

through the data emerging from the Italian Register for HIV infection in children, which was instituted in 1985 by the Italian Association of Paediatrics.^{1 14}

Methods

DATA COLLECTION

Children with HIV-I infection or born to seropositive mothers at 75 participating centres were enrolled in our multicentre study. At the time of writing 1493 children born to HIV-I infected mothers were recorded (828 prospectively followed up from birth). Data were collected through registration and follow up forms as previously described.¹ Information requested included personal data, infection status and clinical condition, mode of delivery and mother's clinical condition at delivery, gestational age, birth weight, and type of feeding. Children were considered breast fed independently from duration. Siblings and twins born to infected mothers were noted. To determine zygosity in twins information on placenta, blood and tissue types, and physical features was requested. These criteria allowed us to establish dizygosity and make a reasonable presumption of monozygosity.^{7 15}

CASE DEFINITION

Infection and clinical status were classified according to the Centers for Disease Control recommendations (P-0, P-1, etc).¹⁶ The infection status was defined by presence/absence of HIV-I antibodies (evaluated by enzyme linked immunoassay and the western blot test^{17 18}) after 15 months of age or, in younger subjects, by a convincing presence of viral markers (p24 antigenaemia,¹⁷ proviral sequences detected by polymerase chain reaction,¹⁸ or repeated viral antigen expression in peripheral blood cells¹⁹) and/or virus isolation from peripheral blood mononuclear cells.²⁰

STATISTICAL ANALYSIS

Data were processed through SPSSX package (SPSS Inc, Chicago, 1986). The relative risk of infection and its significance were calculated through Epi Info Statcalc program (Centers for Disease Control, Atlanta and World Health Organisation, Geneva). Student's *t* test or non-parametric Mann-Whitney tests were used to calculate the significance of differences of means or medians. Differences in frequencies were assessed by χ^2 or Fisher's exact test. Ages

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Table 1 Concordance in infection status according to zygosity in 18 twin pairs perinatally exposed to HIV-I

	Zygosity			Total (n=18)
	Monozygosity (n=5)	Dizygosity (n=8)	Uncertain (n=5)	
Both infected	1	1	2	4
Both uninfected	4	6	3	13
One infected	0	1	0	1
Concordance (%) 5/5 (100)		7/8 (87.5%)	5/5 (100)	17/18 (94.4%)

were reported as median and range. Gestational age and birth weight were expressed as mean (SD).

Results

TWINS

Twenty two twin pairs (22 boys and 22 girls) were recorded with a frequency of 1.5 (22 out of the 1471 total pregnancies). There were 1415 HIV-I infected women. Twenty out of 22 mothers were symptomless at delivery.

Four twin pairs still had an indeterminate infection status (P=0). In 18 pairs the infection status was known, including 10 pairs prospectively followed up from birth.

In the group of twins with known infection status (18 boys and 18 girls aged 16.3 months at the last follow up, range 3.1–60.7 months), nine of the (25%) children were infected. Sex and/or blood and/or HLA typing differed in eight pairs. A reasonable presumption of monozygosity was made in five pairs, whereas zygosity was uncertain in five pairs. Concordance in infection status according to zygosity is reported in table 1. The relative risk of infection in one twin when the other was infected was 23.1 (95% confidence interval 3.3 to 162.1; $p<0.0001$). Infected and uninfected pairs differed neither in gestational age (36.6 (3.1) compared with 35.1 (2.1) weeks) nor frequency of vaginal delivery (2/4, 50% compared with 7/13, 54%). Frequency of infected pairs among those born at a gestational age less than 36 weeks (1/5, 20%) was comparable with that observed in pairs born at or after 36 weeks (3/12, 25%). Birth weight was similar in infected (2167 (336) g) and uninfected (2144 (373) g) twins. In contrast, the proportion of breast fed subjects was significantly higher in infected than in uninfected twins (5/9, 56% compared with 1/27, 4%; $p=0.002$).

Age at last check in infected children was 26 months (range 6–60 months). All HIV-I infected children (two P-1 pairs, two P-2 pairs, and one additional P-2 patient) were surviving.

In one of 10 (10%) pairs prospectively followed up from birth both twins were HIV-I positive. Six pairs (60%) were born by caesarean section, with a frequency comparable with that observed in the whole group. None had been breast fed.

SIBLINGS

Fifty six out of 1415 (3.9%) seropositive women had more than one pregnancy and 115 children (68 boys and 47 girls) were born (including one first born twin pair, one second born twin pair, and one third born child). The presence of

HIV-I related clinical manifestations was recorded in four primiparous women and in five women at second delivery.

Infection status was defined in 41 sibships—that is, 84 children inclusive of one first born twin pair and one third born child. This group included 22 boy and 20 girl first born children aged at the last follow up 38.1 months (range 4.9–93.9) and 30 boy and 12 girl second or third born children aged 16.3 months (range 3.1–60.7). Nine first and 21 second or third born children had been prospectively followed up from birth.

Considering all sibships with known infection status, 26/42 (61.9%) first born and 13/42 (30.9%) second or third born children were infected. On the other hand, when subjects prospectively followed up from birth were taken into account, the presence of infection was reported in an equal proportion of first (2/9, 22.2%) and second or third (5/21, 23.8%) children.

The frequencies of sibships that were concordant or discordant in infection status is reported in table 2. The large majority of discordant sibships included an infected first born and an uninfected second born child. Considering these results from a different point of view (table 3), it was observed that the frequency of infected second born children was significantly higher when the first born was infected than when the first child was uninfected. A 3.1 (95% confidence interval 0.8 to 12.4) relative risk of infection in second born was observed (when the first born was infected) with an at limit significance ($p=0.054$). Information on gestational age, birth weight, type of delivery, and feeding was available in 78 children. Results were comparable in first and second born infected or uninfected children (table 4). The overall frequency of breast feeding, however, was significantly higher in infected (17/36, 47.2%) than in uninfected (9/42, 21.4%; $p=0.03$) siblings.

The frequency of subjects classified as P-2 was comparable in first born (21/26, 80.7%) and second born (10/13, 76.9%) infected children,

Table 2 Concordance in infection status in 41 sibships perinatally exposed to HIV-I

Infection status	Pairs (%)	
Both infected	11 (26.8)	Concordance 24/41 (58.5)
Both uninfected	13 (31.7)*†	
First born infected and second born uninfected	15 (36.5)	Discordance 17/41 (41.4)
First born uninfected and second born infected	2 (4.8)	

*The first born twin pair (both uninfected) were considered as one first born child.

†A third born child was uninfected.

Table 3 Frequency of HIV-I infection in second and third children according to the infection status in first born children

First born child (n=42)	Second or third born child (%) (n=42)
Infected (n=26)	Infected: 11 (42.3)*
	Uninfected: 15
Uninfected (n=16)†	Infected: 2 (12.5)*
	Uninfected: 14‡

* $p=0.047$.

†Including one first born twin pair.

‡Including one third born child.

Table 4 Perinatal data in first, second, and third born children infected or uninfected with HIV-I

	Gestational age (weeks)	No (%) vaginal delivery	Birth weight (g)	No (%) breast fed
Infected:				
First children (n=23)	38.8 (1.8)	20 (86.9)	2979 (574)	12 (52.1)
Second or third children (n=13)	38.8 (2.1)	10 (76.9)	2926 (586)	5 (38.4)
Uninfected:				
First children (n=15)	37.7 (4.3)	14 (87.5)	2910 (564)	3 (20)
Second or third children (n=27)	38.2 (2.6)	23 (85.1)	2973 (478)	6 (22.2)

and no difference was observed as to age at onset of symptoms (15 months, range 1–65 months and 13.5 months, range 1–65 months, respectively). Considering the 11 infected sibling pairs, clinical outcome overlapped in seven (64%) instances (one P–1 pair and six P–2 pairs).

Discussion

Results of the present study clearly demonstrate that twins and second born children of HIV-I infected mothers are not at an increased risk of vertical transmission of the infection. In our country an investigation on 334 first born children identified at birth has recently shown that 19.1% of perinatally exposed subjects are actually infected (C Gabiano *et al.*, unpublished). Comparable or even lower figures in twins and second born children were observed in the present study when, to avoid selection bias, children followed up from birth were considered.

To our knowledge no study has yet determined the risk of perinatal HIV-I infection in twins. Available data on second born children are unreliable because they are based on few cases^{12–13} or on second children of women who had previously given birth to an infected infant.^{10–11} Our study provides figures for counselling seropositive mothers who wish a subsequent pregnancy. It is noteworthy that, despite information and prevention campaigns, some seropositive women plan a second pregnancy.^{10–12}

Up to now discordant infection status had been documented in one monozygotic⁷ and two dizygotic^{8–9} twin pairs born to seropositive mothers. However, our results showed an overall concordance. This finding is not surprising, as twins share factors that have been suggested to influence mother to child HIV-I transmission in utero or at birth: poor clinical condition of the mother²¹ with subsequent high circulating virus load during pregnancy,²⁰ quality of maternal antibody response to HIV-I,^{22–24} length of pregnancy,²² and type of delivery.⁶ In addition, other intrauterine viral infections affecting only one twin have been documented but they are considered exceptional.^{25–26}

Results in the twins and siblings that we studied provide additional information. Vaginal delivery did not increase the proportion of infected children, and consequently caesarean section cannot be considered a tool for preventing infection.⁶ In contrast to a previous report,²² prematurity did not increase the risk of becoming infected. Notably, the group of twins allowed us

to consider a significant number of children born before 36 weeks' gestation. Birth weight was similar in infected and uninfected children. Together with data on gestational age, this finding suggests that HIV-I infection affects neither length of pregnancy nor fetal growth. On the other hand, an increased frequency of breast fed children was observed in infected subjects. This finding is interesting but a selection bias cannot be ruled out. In fact, very few children identified at birth had been breast fed, as in our country most centres counsel bottle feeding for at risk infants. The small number of mothers who were symptomatic at delivery prevented us from considering the role of this variable in favouring vertical transmission. However, it is noteworthy that an equally low proportion of symptomatic women was recorded at first and second delivery suggesting that progression of clinical manifestations after pregnancy is not the rule.²⁷

Our results lead us to speculate that some non-casual factor(s) in the mother and/or the child are crucial in favouring or preventing perinatal HIV-I infection. The role of maternal antibodies to discrete domains of gp120 has been shown.^{23–24} The role of polymorphisms in HIV-I disease progression has been suggested,²⁸ but whether they also influence susceptibility to infection remains to be defined.

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Coroners' records of accidental deaths

Sara Levene

Abstract

This study set out to provide a description of the children involved in fatal accidents and to ascertain which deaths might have been prevented and by what means. The records from a convenience sample of four coroners (jurisdictions of Inner North London, Birmingham, Bedfordshire, and Ipswich) of inquests opened in 1984-8 on children aged under 15 killed in accidents were reviewed for information on the deceased, the accident, and the injuries sustained. Altogether 225 records (150 boys, 75 girls) were examined. Accidents to pedestrians were the commonest cause of death (81 cases), and road safety engineering measures were the most likely means by which most fatalities might have been prevented. The records frequently omitted information on social circumstances, family structure, ethnic group, or the use of safety equipment.

Cooperative coroners can contribute to child safety as their records are rich in information about accidents. This could be made available to parties interested in accident prevention, including community paediatricians.

Accidental death is the largest single cause of death to children aged under 15, and in the UK over 800 children are killed in accidents every year. Some of these cases are thoroughly investigated and considerable information on them is available for analysis, for example, road accidents (from police records). Other sources of data lack uniformity and detail and are not up to date, for example, the Home Accident Deaths' Database.

The only comprehensive source of detailed information on death from all accidental causes is that held in the coroners' records. As has been shown elsewhere, these records contain both basic demographic data (age/sex, etc) and detailed pathological information.¹ An in depth study of these records was undertaken.

Immediate objectives were to provide a detailed description of the children involved in fatal accidents and to ascertain which childhood deaths might have been prevented and by what means. This report also suggests how coroners could contribute more widely to child safety.

Methods

Records from a convenience sample (a presumably unbiased but non-random sample) of four coroners with jurisdictions of different sizes and demographic characteristics were included in

the study. The four jurisdictions were Inner North London, Birmingham, Bedfordshire, and Ipswich.

All inquests opened in 1984-8 inclusive were analysed for children age 0-14. Cases where the verdict was 'accidental death' or 'misadventure' other than medical accidents were included. In addition, records where the verdict was 'unlawful killing', 'death by natural causes', and 'open verdict' were reviewed and included where appropriate. The following information was systematically abstracted, if available:

- The coroner: jurisdiction, record number.
- The deceased: name, address, sex, date of birth, height and weight, ethnic group.
- The family: parent's occupation, family structure.
- The accident: time, day, and date of accident, accident type.
- The injury: nature of injury, treatment received, time to die, abbreviated injury severity score.
- The verdict: cause of death as certified, verdict, notes.

Results

A total of 225 cases was included. These covered Inner North London (87 cases), Birmingham (91 cases), Bedfordshire (42 cases), and Ipswich (5 cases).

PERSONAL DETAILS OF DECEASED

A detailed breakdown into sex and age groups is presented in table 1.

ACCIDENT DETAILS

The various accident types are detailed in table 1, subdivided by age group and sex. There were 91 home accidents, 103 road accidents, and 31 leisure accidents. Of the 225 children, 126 (56%) were playing at the time of the accident. Of 81 pedestrian casualties, 48 (59%) were at play, and sleep was mentioned for 18 children (49%) of the 33 killed by burns or in fires.

POSSIBLE PREVENTATIVE MEASURES

All cases were examined to see whether there were possible measures that might have contributed towards preventing the accident. There were 38 cases where it was considered that no such measures would have been useful. This included a child struck by lightning, three older children who were strangled in accidents that were considered by the coroners to be prank

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Table 1 Type of accident by age and sex

Type	<1 year			1-4 years			5-9 years			10-14 years			All ages		
	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total
Asphyxia*/suffocation/hanging	4	4	8	6	4	10	2	1	3	7	1	8	19	10	29
Burn/scald/house fire	5	4	9	12	11	23	6	0	6	2	1	3	25	16	41
Fall	0	2	2	8	4	12	2	3	5	2	1	3	12	10	22
Drowning	0	0	0	4	3	7	5	0	5	1	1	2	10	4	14
Cutting/piercing	0	0	0	0	1	1	1	0	1	0	1	1	1	2	3
Hit by object†	0	0	0	1	1	2	1	1	2	2	0	2	4	2	6
Pedestrian	0	0	0	16	7	23	20	14	34	19	5	24	55	26	81
Cyclist	0	0	0	0	0	0	2	2	4	9	1	10	11	3	14
Passenger	1	1	2	1	1	2	1	0	1	3	0	3	6	2	8
Bite	0	0	0	0	0	0	1	0	1	0	0	0	1	0	1
Poisoning	0	0	0	4	0	4	1	0	1	0	0	0	5	0	5
Struck by lightning	0	0	0	0	0	0	0	0	0	1	0	1	1	0	1
Total	10	11	21	52	32	84	42	21	63	46	11	57	150	75	225

*Not in fire; †other than car.

imitations of suicide, and older children deliberately crossing major roads in the presence of barriers.

Suggested preventative measures in the other cases were broadly divided into education, engineering, and enforcement. The results are given in table 2. Totals exceed the number of fatalities reviewed, as more than one measure was possibly relevant in some cases.

Because the use of specific safety measures was rarely recorded, it is possible that safety devices were actually in use in some cases but proved ineffective.

MULTIPLE DEATHS

Eighteen children were killed in an accident where more than one person died. These were five house fires, one situation where two cyclists died, and one where two boys playing in a quarry were trapped by falling sand. Only one child was killed in a major disaster (one boy age 7 in the fire at King's Cross tube station).

UNAVAILABLE INFORMATION

Information on children's height and weight was poorly recorded in postmortem data (not available in 142 cases). Information on ethnic group was not available in 88 cases, so no conclusions as to accidents in various racial groups could be drawn. The records also contained very little information about the social and personal details of the children and their families. These shortcomings limited examination of hypotheses linking accident frequency to family size, family structure or position in the family, and social or ethnic background. Information on safety training of children was also limited (for example, cycle training was mentioned in none of 14 cycle accident cases and in cases involving swimming one drowned child was described as a non-swimmer and one as a swimmer).

Discussion

For this study a number of interested and

Table 2 Possible preventative measures

Education	No of fatalities	Engineering	No of fatalities	Enforcement	No of fatalities
General education about child safety:		Environmental design:		Changes in legislation/regulation:	
Adults:		Road safety engineering techniques	58	Combustion modified foam in furniture (now introduced)	14
Scalds—spillage of hot liquid	2	Water—restrict access	9	Flame retardant covers in cars	1
Steam inhalation	1	Window—restrict access	2	Flame resistant nursery products (now introduced)	1
Strangulation of infants	2	Quarry—restrict access	2	Restraints in cars (now introduced)	5
Poisoning	5	Lift—restrict access	1	Restraints for lorry passengers	1
Drowning—toddlers in bath	2	Railings—remove	1	Child resistant closures for all medicines	6
Conflagration—trapped behind locked double glazing	1	Safety products:		Swimming pool isolation	3
Children:		Smoke detectors	20	Bannister design (now introduced)	2
Play with flammable materials	6	Cycle helmets	12	Enforcement of legislation:	
Specific training:		Restraints in cars	5	Offences by drivers	21
Pedestrian safety	27	Reins for toddlers	6	Total	
Bicycle riding and maintenance	10	Window/balcony locks	4	53	
Swimming	5	Stair gate	2		
Driver education	3	Fire guard	2		
Improved supervision:		Swimming pool isolation	3		
Pedestrians	23	Product design:			
Conflagration	10	Foam furniture	14		
Falls from windows or balconies	4	Bannisters	2		
Poisoning	5	Pen caps	1		
Asphyxiation/strangulation	3	Product damage:			
Hit by farm hopper	1	Electrical fault	2		
Drowning	9	Duvet—unstitched thread	1		
Knowledge of first aid:		Product misuse:			
Drowning	13	Smoker's materials (adults)	11		
Asphyxia	6	Double glazing	1		
Scald	2	Steam	1		
Penetrating wound	1				
Total	141	Total	161		

cooperative coroners were willing to open their records for research purposes. It was confirmed that the records do contain much useful information relevant to child safety.

The pattern of accidents observed was as expected from other studies.²⁻⁵ This was true both for the ages and sexes of the children and the accident types. Only one child died in a major disaster, though the occasional mass incident and not the everyday steady stream of deaths receives most publicity.

There was considerable information in the records that did allow suggestions for prevention to be made. Coroners could make this information available at a local level where it could inform local accident prevention groups and community health strategies. It could contribute to a national database on accidental death.

It is inappropriate under the coroners' rules for an inquest to apportion blame.⁶ However, inquests are open to the press who may report on the proceedings, allowing the coroner to make considered public comments that could have an important influence on promoting safety.

Coroners are able to contribute to child safety by opening their records. This should include community paediatricians and other safety workers as well as academic researchers.

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Herpes simplex encephalitis with relapse

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Abstract

Three children are described in whom herpes simplex encephalitis (HSE) followed a clearly biphasic course. The secondary deterioration may be due to a resurgence of the viral infection and calls into question the adequacy of current treatment regimens for HSE. Alternatively, a postinfectious neuroallergic process may be active in which case immunomodulatory treatment might be more appropriate than further antiviral treatment.

There are a number of reports of adults who experienced herpes simplex encephalitis (HSE), that was proved at biopsy, four days to two months after satisfactory response to antiviral treatment.^{1–3} Until recently, only three paediatric cases of relapse have been described^{4–6} of which two^{4,5} were thought to represent post-infectious neuroallergic phenomena. The third case occurred after herpes simplex virus (HSV) type 2 infection in a 6 week old baby and was therefore probably of congenital origin. These have now been supplemented by the description of a further five cases in whom there was evidence to suggest a postinfectious phenomenon (M A Carpentier-Barthez *et al*, paper presented at the European Federation of Child Neurology Societies, Paris 1991). We describe three children who presented with HSE at our hospitals within a two year period and who all experienced a clearly biphasic illness.

Case reports

CASE 1

A previously well 11 year old boy presented to his local hospital with fever, headache, confusion,

and dysphasia. His cerebrospinal fluid was examined (table) and a diagnosis of viral meningitis was made. Over the next few days he became more confused and developed generalised tonic-clonic seizures. A computed tomogram showed predominantly left sided temporal lobe low densities. Treatment was started from the third day of his illness with penicillin and cefotaxime for one week and with intravenous acyclovir (45 mg/kg/day) and dexamethasone for three weeks. His level of consciousness improved and the fever resolved though he was left with a mild right hemiplegia and dysphasia. Eight days after the end of his treatment his fever and headache returned and there was an increase in his dysphasia. Examination of the cerebrospinal fluid was repeated (table) and transfer to a tertiary centre was arranged.

On arrival he was found to be drowsy but rousable with a mild right hemiplegia and a moderate global dysphasia. Extensive microbiological investigations (including cerebrospinal fluid viral culture) were negative with the exception of HSV serology (table). An electroencephalogram (EEG) showed widespread slow activity over the left hemisphere with some intermittent repetitive sharp waves over the left sylvian region, although there were no definite findings to indicate HSE. A computed tomogram showed an enhancing left temporal lesion.

He was treated with a further course of acyclovir (1.5 g/m² surface area/day) followed, in view of the possibility of a resistant organism, by a course of intravenous vidarabine. On this regime his fever, conscious level, and hemiplegia improved. After discharge he is left with a mild right facial weakness and a mild persisting dysphasia.

Findings in blood and cerebrospinal fluid in the three children during the first and second phase of the illness

Day (phase of illness)	Blood (B) or cerebrospinal fluid (CSF)	Protein (g/l)	Glucose (mmol/l)	White cells (×10 ⁶ /l) (% lymphocytes)	Red blood cells (10 ⁶ /l)	HSV titre
Case 1						
3 (1)	B	—	—	—	—	<1/8
3 (1)	CSF	0.31	5	15 (62)	2	<1/2
13 (1)	B	—	—	—	—	<1/8
1 (2)	B	—	—	—	—	=1/64
1 (2)	CSF	1.46	3.9	19 (100)	6	=1/16
Case 2						
1 (1)	CSF	'Normal'	—	0	2	Not done
15 (1)	B	—	—	—	—	=1/60
15 (1)	CSF	—	—	—	—	=1/33
10 (2)	CSF	0.29	2.8	6 (100)	150	=1/16
19 (2)	CSF	0.44	3.6	2 (100)	2800	=1/4
Case 3						
2 (1)	CSF	—	—	20 (35)	—	Not done
4 (1)	CSF	0.7	—	196 (89)	—	Not done
6 (1)	B	—	—	—	—	1/800
19 (1)	B	—	—	—	—	1/25600
19 (1)	CSF	0.96	—	35 (100)	—	1/1600
1 (2)	CSF	1.23	—	63 (100)	—	Not done

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CASE 2

A previously well 9 month old baby presented with a 70 minute generalised seizure in association with fever. Her cerebrospinal fluid was normal. Thirty six hours later she developed a series of right sided seizures for which she was treated with phenobarbitone, penicillin, and chloramphenicol. A computed tomogram was reported as showing a left parietal lobe cerebritis. Transfer was arranged and on arrival she was drowsy but without focal neurological signs. An EEG was suggestive of HSE with runs of discharges particularly over the left temporal region. She was treated with broad spectrum antibiotics and acyclovir, the latter at a daily dose of 1.5 g/m² from the third day of the illness for 10 days.

During her illness a mild right hemiparesis and a conjugate gaze deviation to the left became apparent. By the time of discharge she was standing independently, reaching with a left hand preference, but not smiling. Cerebrospinal fluid at discharge (day 15 of illness) showed anti-HSV titres of 1/33 (titres on serum being 1/60); HSV serology was not available on samples from the beginning of the illness (table). Cerebrospinal fluid viral culture was negative. After discharge she continued to improve, beginning to recognise family members and to smile.

Seventeen days after discharge there was a sudden loss of social contact and the onset of generalised chorea. A repeat computed tomogram showed bilateral temporal lobe low densities which, on a further computed tomogram 14 days later, showed further rostral extension. An EEG showed an appreciably irregular high amplitude slow activity with frequent multifocal discharges most prominent in the temporal regions. A further EEG four weeks later was unchanged. Visual evoked responses and brain stem auditory evoked responses were normal. Further studies of the cerebrospinal fluid were performed on days 10 and 19 of the second illness (table).

Initially she was treated with anticonvulsants with no benefit and then with acyclovir followed by vidarabine as her chorea became more severe during the course of acyclovir. By the end of her antiviral treatment her clinical state remained unchanged and she was then treated with tetrabenazine, pimozide, and benztropine with some benefit. Extensive immunological investigation showed a low IgA concentration of 0.06 g/l (normal range 0.2–0.7 g/l), a low IgG₂ concentration of 0.14 g/l (normal range 0.35–0.87 g/l), and a slightly low phytohaemagglutinin stimulation response of 15.8 µg/ml (normal range >20 µg/ml); all other tests were normal.

At the time of discharge she was severely handicapped with some persisting chorea and no social responsiveness, although there has been some improvement subsequently.

CASE 3

A previously well 11 month old boy was admitted to his local hospital with a 20 minute seizure after 24 hours of fever. His cerebrospinal fluid showed 20 × 10⁶/l white cells (65% poly-

morphs) and he was treated with penicillin, chloramphenicol, and ceftazidime. Left sided seizures started and became intractable, a repeat examination of his cerebrospinal fluid showed an increased pleocytosis (table), acyclovir was started (30 mg/kg/day from the fourth day of his illness), and transfer to a tertiary centre was arranged.

On arrival he was obtunded but with no focal signs. He continued to have left sided seizures which were difficult to control. A computed tomogram showed a low density lesion with patchy enhancement suggesting infarction of the left temporal lobe and adjacent parts of the left cerebral hemisphere. Broad spectrum antibiotics and acyclovir were continued, the latter for 10 days. A repeat computed tomogram on the eighth day of his illness showed extension of the changes to include involvement of the left anterior and posterior cerebral artery territories and of the right middle and anterior cerebral artery territories. Anti-HSV antibody titres in the blood and cerebrospinal fluid were diagnostic of HSE (table). Cerebrospinal fluid viral culture was negative. From the ninth day of his illness he developed continuous choreiform movements of the left limbs.

Six days after the end of his first course of acyclovir he developed further fever and an increased pleocytosis (table), and had a further course of acyclovir this time for 14 days. Herpes serology was not repeated during his second illness.

At discharge he was visually inattentive with a right hemiplegia and a gradually resolving left hemichorea.

Discussion

The biphasic course of the illness in these children may be the result of a resurgence of the viral infection, a postinfectious neuroallergic phenomenon, or a second unrelated and coincidental illness. Extensive investigation has not showed an alternative disease entity. Immunodeficiency seems unlikely as of the two children investigated immunologically only one showed any abnormalities and these were not thought sufficient to explain the clinical course. Furthermore in none of the three children has there been a preceding or succeeding history suggestive of immunodeficiency.

The possibility of viral relapse was not supported by direct evidence of the presence of virus in the second phase of the illness as none of the children had a brain biopsy and the polymerase chain reaction for identification of HSV in the cerebrospinal fluid was not available. The serological findings in case 2 did not show a second rise in titres to support resurgent infection. However there are precedents for a resurgence of HSV that has been proved at biopsy in adults.^{1–3} The good clinical response to a second course of antiviral treatment in case 1 is in favour of this mechanism.

Such a hypothesis calls into question the adequacy of the initial treatment. Case 1 had dexamethasone in addition to acyclovir as part of the treatment for his initial illness and it is possible that this may have had an immuno-

suppressant effect. Alternatively the dose and/or duration of the initial treatment may have been inadequate. All three cases were treated with conventionally adequate HSE regimens. It may be that where there is a confirmed diagnosis of HSE, a 14 day course of high dose acyclovir is more appropriate than a 10 day one.

The alternative postinfectious neuroallergic hypothesis was the presumed mechanism in the seven other non-neonatal paediatric relapses described to date as the specimens from the four brain biopsies performed showed no evidence of persistent virus (M A Carpentier-Barthez *et al*, paper presented at the European Federation of Child Neurology Societies, Paris 1991),^{4 5} and DNA from HSV was not identified in the cerebrospinal fluid at the time of relapse by the polymerase chain reaction in five children (M A Carpentier-Barthez *et al*, paper presented at the European Federation of Child Neurology Societies, Paris 1991). In our case 2 the interval of about two weeks between the two phases of the illness would be more in keeping with this mechanism, though the relapse within days of discontinuing acyclovir in cases 1 and 3 are more suggestive of resurgence of a partially treated infection. The concomitant use of dexamethasone in case 1 might also contribute to this mechanism by suppressing a vasculitic component to the initial process only to allow its emergence as the immunosuppressant effect wears off.

Given the evidence for both viral resurgence and neuroallergic activity in the relapse of HSE it seems likely that the pathophysiology of the second phase of the illness is heterogeneous. Appropriate treatment therefore remains problematic depending as it does on identifying the nature of the process in the individual child. Serological tests do not discriminate rapidly or reliably enough to aid therapeutic decisions. Brain biopsy for culture of HSV would also be

too slow as it may take up to three weeks to grow in this situation. Identification of antigen or DNA in biopsy material would not be sufficient to distinguish between active infection and a postinfectious phenomenon, though its absence from affected brain or cerebrospinal fluid would argue for the latter. Biopsy histology might be helpful but only if brain involved in the second phase of the illness was sampled and the current process identified as either a necrotising encephalitis or a vasculitic picture with perivascular demyelination. Depending on the findings treatment might then include either further acyclovir with or without vidarabine or immunomodulatory treatment such as corticosteroid.

Finally it is of note that two of our three patients relapsed with florid chorea as did all seven of the children with HSE relapse described elsewhere (M A Carpentier-Barthez *et al*, paper presented at the European Federation of Child Neurology Societies, Paris 1991).^{4 5} Case 3 exhibited choreiform movements during the initial phase of the illness. Chorea in association with an encephalopathic illness should raise the possibility of HSE or, in the appropriate context, of HSE relapse.

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Cognitive function after two doses of cranial irradiation for acute lymphoblastic leukaemia

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Abstract
The cognitive function of 23 children given cranial irradiation in a dose of 24 Gy was compared with that of 41 given 18 Gy. No significant differences were found in intellectual function or in mean number of intelligence quotient points lost between patients in the two treatment groups. A reduction in the dose of cranial irradiation does not seem to alleviate long term neuropsychological deficits.

The philosophy of management of childhood malignancy has changed from one of 'cure at almost any cost' to one of 'cure at least cost'. This is exemplified by the treatment of acute lymphoblastic leukaemia in which increasing long term survival brought an awareness of neuropsychological deficits. The cranial irradiation given to treat occult disease of the central nervous system was regarded as the most likely cause of the observed cognitive problems. Because of this the dose of cranial irradiation given to most children in the United Kingdom was reduced in the mid 1980s from 24 Gy to 18 Gy. A previous study in Newcastle showed clear deficits in intellectual function in children with acute lymphoblastic leukaemia treated with 24 Gy when compared both with sibling controls and with children treated for solid tumours who had not received cranial irradiation.¹ A follow up of this initial cohort showed that the deficits persisted.² The same methods have now been applied to a group of children with acute lymphoblastic leukaemia treated with 18 Gy, and a comparison made with the original children treated with the higher dose of irradiation.

Patients and methods

Twenty three children (14 boys and nine girls) treated with 24 Gy and 41 (20 boys and 21 girls) treated with 18 Gy were studied, together with one sibling control for each. Their ages at diagnosis and at time of testing are shown in table 1.

Each child was given the four British Ability Scale subtests appropriate to their age.³ All

Table 2 Mean (SD) IQ before and after treatment and points lost in the two groups

	Irradiation dose	
	24 Gy (n=23)	18 Gy (n=41)
Estimate before treatment	104.3 (4.4)	105.2 (8.8)
After treatment	99.1 (13.2)	100.9 (15.4)
Points lost	5.2 (12.4)	4.3 (12.5)

received the similarities test (verbal reasoning), the matrices test (abstract reasoning), and the recall of digits test (immediate memory). Those over the age of 8 years were also given the speed of information processing test and those less than 8 were given the naming vocabulary test (retrieval and application of knowledge). A pretreatment estimate of intelligence quotient (IQ) was derived using a method described by McNemar,⁴ by which the patient is deemed to have an IQ halfway between the sibling's score and 100—for example, the pretreatment estimate for a child whose sibling scores 130 is 115, and if the sibling scored 90 the pretreatment estimate would be 95.

Results

The results of the full scale IQ assessment are shown in table 2, together with estimates before treatment that were derived from the sibling scores. The mean (SD) loss of IQ in the 24 Gy group was 5.2 (12.4) and in the 18 Gy group 4.3 (12.5). Student's *t* test showed that there was no significant difference between the two groups in the number of IQ points lost.

The *t* test also showed no significant difference in IQ scores between the two groups, and no significant differences in the shape of the profiles calculated for the individual subtests that comprised the IQ measurements in the two groups. A paired *t* test, however, showed that patients in both groups had IQ ratings significantly below those of their calculated estimates before treatment (24 Gy: *p*<0.05, 18 Gy: *p*<0.01).

Discussion

These results indicate that children treated with 18 Gy have deficits that are almost identical to those identified earlier in the 24 Gy group. The reduction in the dose of radiation does not seem to have affected the degree of deficit. Two possible reasons for this could be that there has not been sufficient reduction in dose, or that the deficits are not caused by the irradiation. Several centres in the United States have been

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Table 1 Age of children at time of diagnosis and testing (months)

Irradiation dose	Age at diagnosis		Age at test	
	Mean (SD)	Range	Mean (SD)	Range
24 Gy (n=23)	48.5 (24.1)	16-105	119 (25.8)	88-182
18 Gy (n=41)	56.0 (36.0)	10-162	118.5 (37.0)	55-253

attempting to treat children without irradiation, but giving instead high doses of parenteral and intrathecal methotrexate to treat the occult disease of the central nervous system. Some recent studies have suggested that identical intellectual deficits may also be seen in these children suggesting either that the methotrexate causes similar problems to irradiation, or that intellectual damage might be caused by the disease itself.

There is no unanimity, however, in the reports of intellectual deficits in children with acute lymphoblastic leukaemia. Meadows *et al* were unable to show the same intellectual deficits in children treated with 18 Gy as they had described with 24 Gy.⁵ Eiser has recently reviewed the whole problem of cognitive deficits in children treated for leukaemia.⁶ Clearly they do occur in

many children and for some these are an educational and social handicap. Irrespective of the underlying cause of the problem, remedial help is warranted.

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Congenital neuroblastoma presenting with paraplegia

Fraser D Munro, Robert Carachi, Alasdair H B Fyfe

Abstract

A girl presented with paraplegia at birth. A magnetic resonance scan showed an abdominal neuroblastoma with intraspinal extension. Treatment by chemotherapy did not produce any improvement in the neurological signs. Review of previously reported cases suggests the outlook for neurological recovery is poor regardless of treatment.

Case report

A newborn girl, delivered at 38 weeks' gestation by mid cavity forceps, was noted to have bilateral drop foot, a patulous anus with bulging of the perineum, and bilateral subluxing hips. In the hours after birth she dribbled urine

continuously. Plain spinal x ray films showed expansion of the spinal canal between T12 and L2. A magnetic resonance scan showed an extradural tumour extending from T12 to L3, continuous through the intervertebral foramina with a paraspinal mass on the left side (figure). Her homovanillic acid concentration was 38.8 $\mu\text{mol}/\text{mmol}$ creatinine (normal= <20) and hydroxymethoxymandellic acid 30.4 $\mu\text{mol}/\text{mmol}$ creatinine (normal= <9) supporting a diagnosis of neuroblastoma. A biopsy specimen was taken from the abdominal portion of the tumour at laparotomy. Histology showed this to be a poorly differentiated neuroblastoma. At surgery the liver appeared normal and there were no identifiable lymph nodes. The baby was treated with chemotherapy (vincristine 1.5 mg/m^2 , carboplatin 400 mg/m^2 , etoposide 150 mg/m^2 , and cyclophosphamide 600 mg/m^2).

This was well tolerated but there was no improvement in the neurological signs. Her unstable hips were managed in a Von-Rosen splint and her drop foot by ankle-foot orthoses.

Discussion

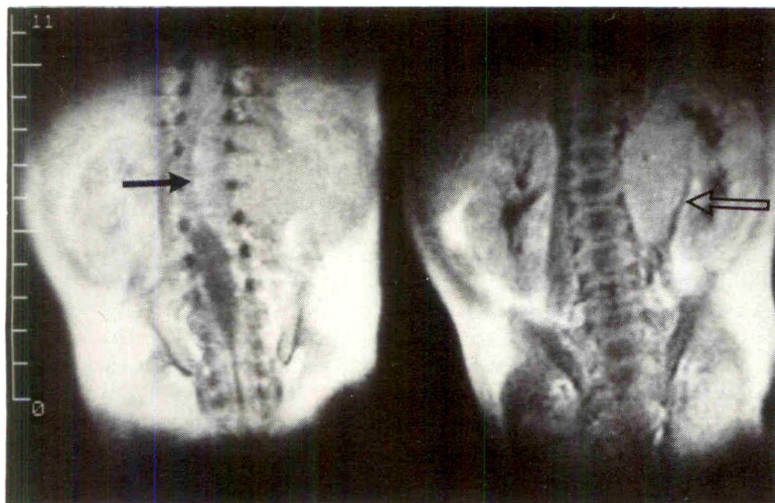
Congenital neuroblastoma presenting with paraplegia is rare. We have found another 15 cases reported in the literature (table).¹⁻³ In all but one case the tumour appeared to be localised at diagnosis, the exception having hepatic metastases. The treatment given was variable. The majority underwent decompressive laminectomy with, in most cases, postoperative radiotherapy or chemotherapy. Two were treated by chemotherapy alone and none by radiotherapy alone, and one by vitamin B-12 alone. Survival appears good with only two deaths; however, the neurological outcome was very poor.

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Magnetic resonance scan showing paraspinal tumour (open arrow) with intraspinal extension (black arrow).

Congenital neuroblastoma with paraplegia

Author*	Age at diagnosis	Treatment	Outcome	Neurological outcome	Follow up period (years)
Moschos and Anagnostakis (1975)	6 Days	Laminectomy, chemotherapy	Alive	Improved sphincter tone, paraplegic	1·9
Kenney <i>et al</i> (1982) ¹	5 Weeks	Chemotherapy	Died	No improvement	0·3
	Not known	Laminectomy, chemotherapy	Died	No improvement	0·3
Bodian (1963)	10 Months	Laminectomy, vitamin B-12	Alive	No improvement	2·3
	3 Weeks	Biopsy, vitamin B-12	Alive	No improvement	6·6
	6 Days	Laminectomy, radiotherapy, vitamin B-12	Alive	No improvement	1·8
Katcher (1952)	3 Weeks	Laminectomy, radiotherapy, chemotherapy	Alive	Improved sphincter tone, persisting limb weakness	0·3
Hrabovsky and Jones (1979)	2 Weeks	Laminectomy, chemotherapy	Alive	No improvement	1·0
Elefant <i>et al</i> (1958)	1 Month	Laminectomy, radiotherapy	Alive	Improved sphincter tone, persisting limb weakness	1·7
Punt <i>et al</i> (1980) ²	3 Days	Laminectomy, radiotherapy	Alive	No improvement	14·0
	1 Day	Laminectomy	Alive	No improvement	11·0
	4 Months	Laminectomy, radiotherapy	Alive	No improvement	7·0
	2 Weeks	Radiotherapy, chemotherapy	Alive	No improvement	4·0
Haden and Keats (1983) ³	1 Month	Laminectomy, radiotherapy	Alive	Residual weakness of left leg	32·0
Rothner (1971)	2 Days	Laminectomy, radiotherapy	Alive	No improvement	0·8
Munro <i>et al</i> (1991)	3 Days	Chemotherapy	Alive	No improvement	0·8

*The full references for those publications not included in the list of references at the end of the paper can be obtained from Kenney *et al*,¹ Punt *et al*,² and Haden and Keats.³

Twelve patients showed no improvement in their neurological signs after treatment and four showed some improvement but were still left with significant neurological deficits. The method of treatment or the time from birth to treatment did not seem to be different between those showing some recovery and those with none. By comparison series of older children with cord compression from neuroblastoma show poorer survival, particularly in those over 1 year of age at presentation, but a much better neurological outcome. Series of patients treated both surgically^{2 4 5} and by chemotherapy alone⁶ have shown neurological recovery in 40–80% of cases. Surgery is not without its complications: significant spinal deformity is reported as affecting up to 60% of survivors after laminectomy.^{4 5} Given this high morbidity and the seemingly poor prognosis for neurological recovery we

would question the usefulness of laminectomy in congenital neuroblastoma with paraplegia. We would postulate that in this group cord compression must occur antenatally and that by the time of birth, irreversible damage has already occurred.

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Omenn’s disease

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Abstract
The importance of accurate pathological diagnosis is emphasised in the case of a newborn infant who presented with alopecia, a generalised erythrodermatous skin eruption, and hepatosplenomegaly. She subsequently developed generalised lymphadenopathy and recurrent septicaemia and died aged 2 months. The histological findings of widespread lymphocytic, histiocytic, and eosinophilic tissue infiltration, associated with thymic hypoplasia, were consistent with autosomal recessive Omenn’s disease.

Omenn’s disease is a rare autosomal recessive reticuloendotheliosis of infancy with similarities

to many other reticuloses but with several distinguishing features of genetic and therapeutic importance. We are unaware of any previously reported cases in the United Kingdom.

Case report

The index case was a girl who was the first child of non-consanguineous parents. The pregnancy and delivery were uncomplicated and her birth-weight was 2830 g. Hair was seen in the liquor and remaining scanty scalp hair was wiped off when she was dried. There was no other bodily hair but a generalised dry scaly rash was present with flexural cracking and extensive serous exudation. Liver and spleen were both palpable 2 cm below the costal margins and the abdomen

was mildly distended. There were no other problems initially and she was successfully breast fed. After the first week, however, there was progressive deterioration with widespread lymphadenopathy, diarrhoea, ascites, and intolerance of feeds. Five separate episodes of septicaemia were recorded with *Escherichia coli* or *Staphylococcus epidermidis*.

Relevant investigations included: peripheral white cell count of $8.2 \times 10^9/l$ (neutrophils $1.9 \times 10^9/l$, lymphocytes $4.9 \times 10^9/l$, monocytes $0.3 \times 10^9/l$, eosinophils $1.1 \times 10^9/l$). Serum albumin concentration was 26 g/l and globulin 9 g/l. Her concentrations of immunoglobulins were (normal range): IgA 0.3 g/l (0.02–0.15 g/l), IgG 2.5 g/l (3.9–13.0 g/l), and IgM 0.2 g/l (0.09–0.4 g/l). Lymphocyte T and B cell ratios were normal but the thymic shadow was absent on chest radiography. Extensive investigations for metabolic and infective causes were unhelpful.

Examination of bone marrow revealed a normocellular marrow with an increased myeloid:erythroid ratio of 4:1 and abnormally high representation of eosinophilic precursors at 12%. A skin biopsy specimen revealed a band-like lymphocytic infiltrate in the upper dermis with occasional histiocytes and eosinophils. Basal layers of epidermis were involved with exocytosis spongiosis and eosinophilic bodies. Lymph nodes showed considerable depletion of normal lymphocytic populations, the parenchyma displaying prominent nodules of histiocytes. A few poorly cellular follicles remained and intervening fibroblastic stroma contained lymphoid cells, plasma cells, and eosinophils. A liver biopsy specimen revealed non-specific changes with mild fibrosis, cholestasis, and proliferation of biliary ductules. A rectal biopsy specimen displayed normal crypt architecture with normal lymphoid aggregates, and placental histology was unremarkable.

Initially the erythroderma responded to simple emollients with improvement in the cracking and scaling, although the skin remained taut shiny and erythematous. The child failed to gain weight despite the parenteral nutrition, had repeated episodes of septicaemia, and developed progressive ascites. Cardiac failure developed in association with an episode of septicaemia and she died at 2 months of age. In addition to the previous histological findings, postmortem examination demonstrated hypoplasia of the thymus with absent Hassall's corpuscles.

Discussion

The familial histiocytic reticuloses comprise a heterogeneous group of disorders in which the major feature is a proliferation of reticuloendothelial cells with infiltration of tissues. Classification remains difficult and the overlap of

some features such as histiocytic infiltration has led to the confusion of different diseases within the group, particularly familial haemophagocytic reticulosis and Letterer-Siwe disease.

Omenn described 12 infants in whom the major features were onset in the first month of a severe skin eruption followed by hepatosplenomegaly, lymphadenopathy, hypogammaglobulinaemia, and eosinophilia.¹ Failure to thrive and recurrent febrile illnesses progressed to a fatal outcome within six months in all cases. Skin, lymph node, and bone marrow examinations were virtually identical to those described in our case. Similar findings have subsequently been reported,^{2,3} though not previously in the United Kingdom. Further immunological defects, since outlined, include thymic hypoplasia and defective cell mediated immunity.^{3,4}

Familial haemophagocytic reticulosis was first described by Farquhar and Claireaux in 1952,⁵ since when several further cases have been reported. Although histiocytic infiltration of many tissues does occur in this condition the disease is characterised by the phagocytosis of blood cells by histiocytes, a pancytopenia, and in many cases an encephalitic process. Letterer-Siwe disease shares some common features with Omenn's disease, including seborrhoeic skin eruption and tissue infiltration by histiocytes, but is distinguished by its pancytopenia and lack of eosinophilia.

The features of eosinophilia in peripheral blood and bone marrow combined with early presentation of disease characterised by seborrhoeic skin eruption, hepatosplenomegaly and widespread lymphadenopathy, hypogammaglobulinaemia, susceptibility to infection, and rapidly fatal course appear to be unique to Omenn's disease.

The importance of the accurate diagnosis of this condition goes beyond the greater understanding of the disease processes involved. The inheritance has been shown to follow an autosomal recessive pattern in some families,¹ so that the recurrence risk of one in four is considerably greater than for other reticuloses. In addition successful treatment with bone marrow transplantation has now been described.⁶

Our thanks to Drs M Malone and B Favarra for reviewing histological sections.

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Outcome in tyrosinaemia type II

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Abstract

Tyrosinaemia type II was diagnosed in a boy with failure to thrive and in his sister on neonatal screening. On diet the outcome, at 12 and 10 years respectively, has been excellent in respect of oculocutaneous sequelae, growth, and psychomotor development, contrasting with the generally unfavourable outcome in most reported cases.

Oculocutaneous tyrosinaemia (first described as the Richner-Hanhart syndrome) and now designated tyrosinaemia type II is due to deficiency of hepatic cytosolic tyrosine aminotransferase. The gene defect has recently been localised to chromosome 16. Clinically there is a variable combination of hyperkeratotic skin lesions, keratoconjunctivitis, and mental retardation.¹

This report documents clinical and biochemical findings in two further cases under long term follow up, in whom serious sequelae appear to have been avoided by early institution of a low tyrosine diet.

Case reports

DIAGNOSIS

The index case (case 1) was the first child of unrelated Scottish parents, male, born at term, with a birth weight of 3700 g. At 3 months of age, after difficulties in breast feeding, he was changed to formula feeds. His progress from 3 to 5 months was characterised by slow feeding, vomiting, irritability, drowsiness, and deterioration in weight from the 50th to the 3rd centile. A plasma tyrosine concentration of 1300 $\mu\text{mol/l}$ (reference range 30–100) and an increased urinary excretion of tyrosine were the only abnormalities found. At 8 months of age a low tyrosine diet was instituted and within days the infant improved.

The second child (case 2) of the same parents was female, full term, and weighed 4000 g. On breast feeding at 4 days of age plasma tyrosine concentration was 705 $\mu\text{mol/l}$, rising to 1340 $\mu\text{mol/l}$ at 18 days, and a low tyrosine diet was commenced.

At presentation both children had normal liver function tests, normal plasma methionine, and no generalised aminoaciduria. On restricted diet with plasma tyrosine concentrations of 400–800 $\mu\text{mol/l}$ both children had abnormal urinary excretion of p-hydroxyphenyllactic, p-hydroxyphenylpyruvic, and p-hydroxyphenylacetic acids. N-acetyl tyrosine was identified by gas chromatography-mass spectrometry. Succinyl acetone and delta amino laevulinic acid excretion in urine were within normal limits.

Ascorbic acid, used in transient neonatal tyrosinaemia,¹ was tried in a dose of 200 mg

three times a day on case 1 at the age of 2 years with no effect on plasma tyrosine. Pyridoxine, the cofactor of tyrosine aminotransferase,¹ in a dose of 50 mg three times a day, was also ineffective.

DIET

The protein substitute has been a low phenylalanine/tyrosine free amino acid mixture (Code 114, Scientific Hospital Supplies) supplemented with Ketovite liquid and tablets (Paines and Byrne) and metabolic mineral mixture (Scientific Hospital Supplies). Protein was given as 1g exchanges at mealtimes. With age the number of exchanges has gradually increased from four to 12 and has been titrated against the plasma tyrosine response. When the diet was introduced plasma phenylalanine concentration fell to <25 $\mu\text{mol/l}$. Increasing the number of protein exchanges resulted in plasma tyrosine concentrations of greater than 1000 $\mu\text{mol/l}$. Acceptable phenylalanine concentration without undue hypertyrosinaemia was achieved by giving daily supplements of 500–800 mg phenylalanine. Protein free or low protein foods have been allowed freely.

PROGRESS

In the early years both children had repeated episodes of photophobia with eye pain, redness and watering, often triggered by intercurrent infection and usually with plasma tyrosine concentrations in excess of 800 $\mu\text{mol/l}$. During acute episodes ophthalmological examination showed that both children had bilateral keratopathy resembling dendritic ulceration due to herpes simplex infection. The number of protein exchanges in the diet was cut by up to 50% at the earliest sign of eye discomfort.

Biochemical monitoring of tyrosine concentrations (figure) shows fluctuating control in the range 300–800 $\mu\text{mol/l}$ with occasional peaks of up to 1000 $\mu\text{mol/l}$.

At 12 years case 1 was on the 50th centile for height and weight. His eye symptoms had become less frequent and less severe with no overall change in plasma tyrosine concentrations. On psychometric testing using the Wechsler intelligence scale for children, standardised for Scotland (WISC-RS), he showed overall average ability scoring 98 (45th centile) on the full scale, with a discrepancy (significant at the 5% level) between the verbal scale score 85 (16th centile) and the performance scale score 115 (84th centile).

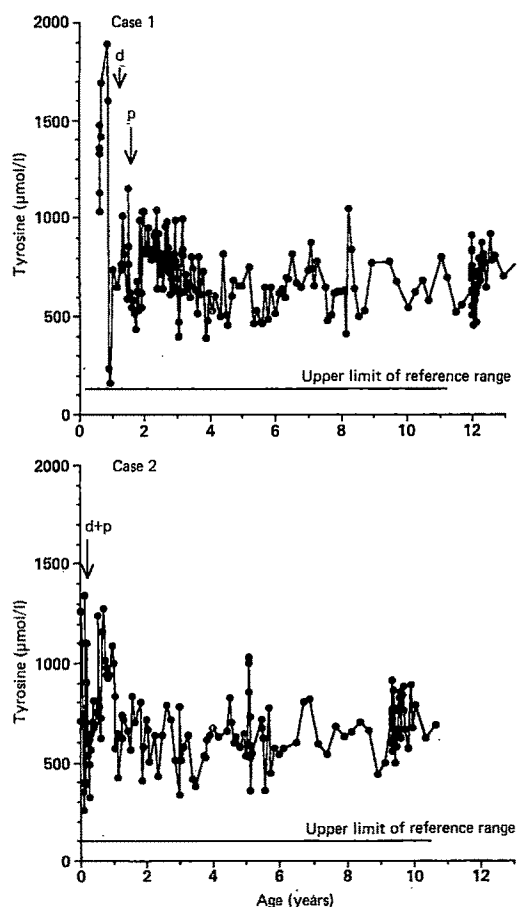
At 10 years case 2 was on the 75th centile in height and the 97th centile in weight. Bouts of mild conjunctivitis continued to occur every three to six months and responded to temporary further reduction in tyrosine intake. She was

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Plasma tyrosine concentrations when diet was controlled; d and p indicate introduction of diet and phenylalanine supplementation respectively.

within the average range of ability in the WISC-RS scoring 92 (27th centile) on the full scale, with a verbal scale score of 96 (40th centile) and a performance scale score of 89 (23rd centile).

Both children have normal visual acuity, no significant refractive error, and only minimal scarring from the previous pseudodendritic ulcers.

They are making normal progress in mainstream education at a level consistent with parental ability. The father is self employed as a graphic designer and the mother is a housewife and part time secretary.

Discussion

The clinical and biochemical findings are consistent with tyrosinaemia type II. Diagnostic liver biopsy was not justified. Attempts to identify a point mutation at the tyrosine aminotransferase locus² in this family are currently being undertaken (G Scherer, personal communication).

Buist *et al* estimated that about 80% of cases have skin lesions, 75% eye disease, and 60% intellectual retardation.³ Age at presentation varied from the newborn to adult. Our index

case was diagnosed as the result of investigation of failure to thrive in infancy at a time when he had none of the characteristic clinical features.

Typically, bullous cutaneous lesions develop on the extremities and crusting leads to hyperkeratotic patches. These painful lesions clear up rapidly on controlling the hypertyrosinaemia. Our cases have never developed any cutaneous stigmata.

Eye lesions are extremely distressing with photophobia, intense burning pain, inflamed conjunctivae, and herpetic-like corneal ulceration. Residual damage can occur with dense corneal scarring, neovascularisation, and visual impairment. In our patients on diet episodes of keratoconjunctivitis occurred at times of intercurrent infection and usually, but not invariably, with plasma tyrosine concentrations of >800 µmol/l. Symptoms responded rapidly to further temporary restriction of tyrosine intake and no significant corneal damage has resulted.

The mechanism of brain damage is not known. A range of neurological outcome is reported from normality, through defects in fine coordination and language skills, to microcephaly, self mutilation, and gross retardation. The incidence of mental defect may partly reflect ascertainment bias in the selection of cases studied. Maternal tyrosinaemia type II has been associated with normal³ and microcephalic⁴ progeny. Our patients at follow up show overall average ability in psychometric assessment.

Genetic heterogeneity in tyrosinaemia type II may be responsible for some of the variation in manifestations and prognosis, but in our cases there is a reasonable presumption that long term control of hypertyrosinaemia was responsible, at least in part, for the satisfactory outcome. Goldsmith and Laberge have emphasised the lack of information on the optimal timing of diet and the degree of control needed to achieve the best results.¹

Along with two cases reported by Halvorsen,⁵ our patients show that with early detection, effective diet, and careful biochemical surveillance, this form of tyrosinaemia can have a good prognosis.

We acknowledge the assistance of Dr JM Rattenbury, Children's Hospital, Sheffield, who made the initial biochemical diagnosis and Jean Bechhofer, clinical psychologist, Royal Hospital for Sick Children, Edinburgh, who carried out psychometric assessments.

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CURRENT TOPICS

Immunisation of infants against *Haemophilus influenzae* type b in the UK

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Haemophilus influenzae is one of the micro-organisms that make up the commensal flora of the upper respiratory tract. Carriage is common, but compatible with good health. None the less, *H influenzae* is a pathogen and, in the case of encapsulated type b organisms, causes life threatening, invasive (bacteraemic) infections, the most common and serious being meningitis and epiglottitis (table 1).¹ The type b capsule is a crucial virulence factor and is composed of polyribosyl ribitol phosphate (PRP).² Serum antibodies to the type b capsule can protect against invasive disease but immunocompetence generally takes some years to mature.³⁻⁵ Young children are therefore particularly susceptible to *H influenzae* type b and its potential to disseminate through the bloodstream (70% of cases occur in infants less than 2 years old).⁶ During the past two decades intensive efforts have been made to develop a vaccine that could hasten the onset of protective immunity with the goal of eliminating most serious *H influenzae* type b infections. There has been spectacular progress and this seems an opportune time to summarise the future of *H influenzae* type b immunisation in the UK.⁷

The crucial science that has been applied to developing effective vaccines against *H influenzae* type b for use in infants stems from observations made more than 60 years ago.⁸ Purified polysaccharides, such as PRP, are poor immunogens when used in their natural state and especially in children less than 2 years old.³ By linking the polysaccharide PRP chemically to a protein carrier, however, a conjugate

vaccine is produced that can provoke a serum antibody response to the polysaccharide, which is sufficient to protect against disease. Importantly, this response displays immunological memory—that is, it has a boosting effect when there is re-exposure to the relevant antigen. Four *H influenzae* type b conjugate vaccines have so far been developed (table 2),⁹ and each has been evaluated in clinical trials. Infants in these studies received either two or three doses of conjugate vaccine by intramuscular injection between the ages of 2 and 6 months. Comparison of data obtained for the different lots of any one vaccine (for example, PRP-D) in different studies or for the different vaccines (even in the same country) are not valid because of many uncontrolled variables (for example, population immunised, number of doses of vaccine, antibody assay used, and so on). In all cases the conjugate vaccines resulted in significantly higher titres of total serum antibody to type b capsule than would have been expected in infants who had not been immunised. In general, a level of >0.15 µg/ml correlates with protection in the short term.

Although it is too early to judge conclusively the relative merits of these vaccines, all four seem to be suitable for use in infants. Important and unequivocal variations in immunogenicity have, however, been shown, and it is likely that these differences will correlate with each vaccine's relative ability to prevent disease.¹⁰

Is a vaccine against *H influenzae* type b needed in the UK?

Epidemiological data from regional surveys of microbiologically confirmed infection have shown that the probability of a child contracting invasive *H influenzae* type b disease in the UK by the age of 5 is about 1:600, and the probability of it being *H influenzae* type b meningitis

Table 1 Carriage and pathogenicity of *H influenzae*

Strains of <i>H influenzae</i>	Common rates of upper respiratory tract carriage	Principal signs of pathogenicity
Non-encapsulated	50-80%	Exacerbations of chronic bronchitis, otitis media, sinusitis, and conjunctivitis; patients commonly adults; bacteraemic infections rare but may occur in neonates
Encapsulated type b	2-4%	Meningitis, epiglottitis, pneumonia and empyema, septic arthritis, cellulitis, osteomyelitis, pericarditis, bacteraemia; rarer signs include glossitis, tenosynovitis, peritonitis, endocarditis, and ventriculitis, associated with infected shunt tubing
Encapsulated types a, c, d, e, and f	1-2%	Rarely incriminated as pathogens

Adapted from Turk with permission.¹

Table 2 Immunogenicity of *H influenzae* type b conjugate vaccines

Vaccine and manufacturer	No of infants immunised	Country	Geometric mean titre of serum antibodies to type b capsule (µg/ml)*
PRP-D (Connaught Laboratories)	64	USA	0.53
	72	Finland	0.63
PRP-T (Pasteur-Merieux)	117	France	4.80
	81	Chile	11.32
PRP-OMP (Merck, Sharp and Dohme)	475	USA	4.63
HbOC (Lederle-Praxis)	163	USA	16.84
	46	Finland	4.37

Reproduced from Moxon and Rappuoli with permission.⁹
*Measured by radioimmunoassay at about 7 months.

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is 1:850⁶ (AJ Howard, personal communication). There are about 65 deaths each year.⁶ Comparative rates for representative European countries, and states in North America and Australia indicate that the problem of *H influenzae* type b meningitis in the UK is similar to that reported elsewhere in the western world (table 3).⁷

Few reliable data are available about morbidity, especially concerning the apparently permanent effects on the central nervous system that have been reported elsewhere in children who have survived episodes of *H influenzae* type b meningitis.¹¹ Devastating damage to the central nervous system occurs in a minority, but sensorineural hearing deficits are likely to be a problem in about 6% of children who recover from *H influenzae* type b meningitis.¹² It is likely that many undetected, or unreported, neurological deficits occur (for example, motor incoordination, deficit in intelligence, or learning difficulties) as a result of *H influenzae* type b meningitis, but there have so far been no prospective studies published for the UK. Overall, the impact of *H influenzae* type b infection, especially meningitis, seems to be comparable with that of poliomyelitis before the introduction of routine immunisation.¹⁰ Polio occurred in epidemics, however, and young adults were particularly prone to serious disease. These patterns of disease are more analogous to infections with meningococci, which have attracted much attention from the media in recent years and resulted in considerable anxiety in affected communities. Because *H influenzae* type b infections occur sporadically, this may explain in part why they have attracted less attention than would seem merited. In every year since 1982 (when the Office of Population Censuses and Surveys began reporting cases of both meningococcal and *H influenzae* type b meningitis) the incidence of *H influenzae* type b meningitis in children in the UK has been greater than that of meningococcal meningitis.¹³

Additional concerns are that there has been an absolute increase in the incidence of *H influenzae* type b infection in the UK over the past decade,¹³ and primary resistance to antibiotics may lessen the effectiveness of treatment. About 11% of isolates of *H influenzae* type b are now resistant to ampicillin (there was none before 1974) and rare instances of resistance to chloramphenicol have been reported.¹⁴

There is, therefore, a compelling case for routine immunisation against *H influenzae* type

b infection providing that the proposed vaccine is safe, highly effective, compatible with our existing routine immunisation programme, and not prohibitively expensive.

Are vaccines against *H influenzae* type b safe?

Extensive investigations have shown that the four vaccines are tolerated well and serious adverse effects do not occur.^{10 15} *H influenzae* type b conjugate vaccines are already used routinely for infants in the USA, Finland, Iceland, and Germany. It can be concluded with confidence that *H influenzae* type b conjugate vaccines are among the safest bacterial vaccines ever proposed for routine use. It should be anticipated, however, that serious illnesses or unexpected deaths (for example, cot deaths) may occur that are temporally related to, but not caused by, immunisation.

Are vaccines effective against *H influenzae* type b?

Trials have established that vaccines against *H influenzae* type b are immunogenic at all ages from 2 months or older.^{9 10} There are several important variables which affect the immune response, however, and these include: age at which the primary series of two or three immunisations is given, interval between each dose of vaccine, and the choice of conjugate.¹⁰ The immune response may also be influenced by genetic factors.¹⁶ In general, PRP-D has proved to be the least immunogenic in infants; PRP-OMP and, to a lesser extent, PRP-T stimulate a substantial antibody response after the first dose, whereas HbOC and PRP-D do so only after the second dose. The response to booster doses is least strong for PRP-OMP.

Although these comparisons of immunogenicity are helpful as indicators of the potential of each vaccine, the important criterion is the extent to which vaccines against *H influenzae* type b prevent disease. Efficacy studies have shown that PRP-D, HbOC, and PRP-OMP can prevent more than 90% of *H influenzae* type b disease.^{5 7 15} A formal efficacy study of PRP-T has not been completed, but this vaccine is currently offered as a routine vaccine to all children in Finland, and its efficacy is also being evaluated in the UK. PRP-D proved to be ineffective in preventing *H influenzae* type b disease in a trial of its efficacy among Alaskan children.¹⁷ Its relatively lower immunogenicity, combined with certain epidemiological characteristics of *H influenzae* type b disease in Alaska, make it likely that this disappointing result could be reversed by the choice of a different conjugate—a possibility that is supported by the excellent results obtained with PRP-OMP among native American Indians in Arizona.¹⁵

Is immunisation with *H influenzae* type b conjugate vaccine compatible with the existing routine immunisation schedule?

Extensive studies elsewhere have documented the feasibility of giving vaccine against *H*

Table 3 Incidence of *H influenzae* type b meningitis in developed countries

Country	Yearly incidence of <i>H influenzae</i> type b meningitis/100 000 children aged <5 years
USA: Texas, Minnesota, California, North Carolina, and Maryland	19-67
Finland	26
Netherlands	22
Sweden	31
UK	24
Australia: Victoria and New South Wales	20-25

Modified from Vaccine with permission.⁷

influenzae type b at the same time as the routine immunisations against diphtheria, pertussis, tetanus (DPT), and polio.⁵ Given the recent modifications to the UK schedule,¹⁸ it is important to study carefully the use of vaccines against *H influenzae* type b that are given at 2, 3, and 4 months because other studies (excluding one recent one) have not precisely duplicated this schedule. Preliminary results suggest that responses of children in the UK using the accelerated schedule are excellent and further studies should expand on these data during the next few months.¹⁹ It is also possible that vaccine against *H influenzae* type b could be given in the same syringe mixed with DPT rather than as a separate injection—a sensible innovation that could potentially further increase the acceptability of the vaccine, and make routine immunisation against *H influenzae* type b more convenient to give. The issue of the possible need for booster doses will also require some investigation, but there are insufficient data at present about the duration of protection after immunisation of young infants.

How will it be known whether *H influenzae* type b conjugate vaccines are acceptable and effective?

Relevant to both questions will be the accurate documentation of vaccine uptake. No vaccine can be successful if it does not reach the target population. Thus the much needed improvements in our current routine immunisation programme that have occurred recently, and the improved monitoring of uptake of vaccination, are important tools for evaluating the success of the introduction of *H influenzae* type b vaccination. Systematic reporting of episodes of invasive (bacteraemic) *H influenzae* type b infections may be based upon the current Communicable Disease Surveillance Centre laboratory reporting system. There is, however, a recent initiative through the Public Health Laboratory Service (PHLS) to provide more detailed prospective data on the incidence of *H influenzae* type b infection in six regions of England and Wales. Scotland has maintained an independent and relatively complete system for recording invasive *H influenzae* type b infections. It should therefore be possible to gauge the impact of routine *H influenzae* type b immunisation by monitoring the incidence of disease and relating these data to our past experience.

Despite obvious weaknesses, this approach to assessing the effectiveness of vaccination is probably the only practical option in the UK. Placebo controlled studies are no longer ethical. Prospectively designed efficacy trials are difficult to organise and their cost can be prohibitive.⁷ (A prospective open implementation study of PRP-T vaccine involving sequential introduction of vaccine at a district level is underway in the Oxford region in anticipation of the national introduction of *H influenzae* type b immunisation, which will be late in 1992.) Given primary efficacy data on three of the four *H influenzae* type b conjugate vaccines, and implementation studies on the fourth

(PRP-T),* it seems sensible to invest in a prospective registry of cases of *H influenzae* type b infection in both immunised and unimmunised children, which could then be analysed in a case control manner. For this, it will be essential to ensure that episodes of *H influenzae* type b disease are fully documented and that the disease isolates are verified at an appropriate PHLS reference laboratory.†

Conclusion

The successful development of *H influenzae* type b conjugate vaccines is a milestone in the control of microbial diseases. The achievement is especially noteworthy in that these conjugate vaccines elicit in infants specific immune responses that are greater than those achieved by natural exposure to *H influenzae* type b (or cross reactive bacteria) irrespective of whether asymptomatic carriage or invasive disease resulted from the natural exposure. Because the immune response of infants to native capsular polysaccharides is often too slight to result in protection, the exploitation of the hapten carrier principle to formulate conjugate vaccines opens the door for development of other conjugate polysaccharide vaccines for the prevention of bacterial meningitis and invasive infections caused by encapsulated bacteria such as pneumococci, meningococci, coliforms, and group B streptococci. Finally, *H influenzae* type b disease is a global problem, so the successful implementation of conjugate vaccines in industrialised countries can pave the way for their use in developing countries.

*Clinical experience with 70 000 children immunised has shown no cases of infection after either two or three doses of a three dose primary schedule (B Fritzell, personal communication).

†The recognised PHLS reference laboratory for haemophilus is at the John Radcliffe Hospital, Oxford.

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Child poverty and deprivation in the UK

N J Spencer

There has been more than a decade of debate about the increase in child poverty during which the former Secretary of State, John Moore, announced 'the end of the line for poverty' (speech text 11 May 1989). Recently the National Children's Bureau has published an authoritative and well documented account commissioned by Unicef for a comparative study of child poverty in the industrialised countries.¹

The association of poverty with childhood mortality and ill health is well established in developing countries² and it is broadly accepted that the major determinants of improved health in developed countries have been better living conditions, sanitation, and higher standards of living.³ Against an overall trend of continuing improvement in mortality, inequalities of health outcomes between social groups persist and, indeed, may be widening.⁴

Poverty and inequality in the 1980s

No official poverty line is accepted in the UK. The concept of 'relative poverty', as defined by Townsend,⁵ has been used by most researchers. The numbers of children living in relative poverty increased sharply between 1979 and 1987. From 1979 to 1985 there was a 110% increase in children living in families dependent on supplementary benefit and a 25.7% increase in children in families with incomes below 50% of the average.¹ In 1985, 3.5 million children were living in or 'on the margins of' poverty.¹

Families with children have displaced pensioners as the largest single group in poverty.¹ The 'trickle-down' effect, by which the poor were supposed to benefit from the general increase in prosperity, has conspicuously failed. In terms of final income the share of the lowest fifth fell from 7.1% in 1979 to 6.3% in 1987 and the highest fifth rose from 38 to 42%.⁶ The disposable income of the lowest income decile has actually fallen in real terms over the decade: lone parents with one child have suffered a loss of >25% and couples with three or more children a loss of 15%.⁷

The causes of child poverty in the 1980s

Bradshaw identifies economic trends, demographic changes, and social policies as contributing to the increase in prevalence of child poverty in the 1980s.¹

ECONOMIC TRENDS

Unemployment, short and long term, increased sharply and reached 3.7 million in 1985-6. The

subsequent fall, assisted by a total of 27 changes in the counting method, left pockets of high unemployment in many areas and the rates have increased again since April 1990. Low pay, affecting particularly women and the young in unskilled jobs, has increased. The number of wage earners falling below the Council of Europe's 'decency threshold' increased from 7.8 to 9.9 million.¹

DEMOGRAPHIC CHANGES

The proportion of lone parent families doubled to 14% of all families with children between 1961 and 1986. There are now more than one million families headed by a lone parent, 90% of whom are women, containing 1.6 million children. An estimated one third of children will experience living in a lone parent household during their childhood.⁸ The rising divorce rate, peaking at 12.7/1000 married people in 1985 and particularly affecting younger marriages, and the increase from 9.2% in 1976 to 27% in 1989 of children born outside marriage have both contributed to this trend. The incidence of poverty is much higher in lone parent families with an estimated 70% living in or on the margins of poverty.⁹

SOCIAL POLICY

Social policy in the 1980s has been shaped by the commitment of the government to reductions in taxation and public spending. Paradoxically, public spending has risen in real terms and taxation changes have benefited only those on higher incomes.¹⁰ Changes in the social benefits system, in particular the freezing of universal child benefit and the replacement of extra single payments by the loan based social fund, shown to increase, rather than reduce, indebtedness,¹¹ have affected low income families with children disproportionately.

Children in low income families have been affected by the reduction in public expenditure on housing. This reduction, along with other aspects of housing policy, has resulted in a major increase in homelessness with nearly 100 000 households involving children registered homeless in 1988.¹² Constraints on education expenditure have limited services, notably school meals and preschool provision, from which poor children would be expected to benefit.¹

The 1989 Children Act, due to come into force in October 1991, has been welcomed as the most comprehensive reform of child law this century but, even here, severe financial con-

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straints on local authorities could jeopardise its implementation unless additional funding is made available.

Effects on children's health

MORTALITY

The decline in mortality rates of children has continued in the 1980s. However, UK infant mortality rates have declined more slowly than those in other European countries¹ and social inequalities in infant mortality show no sign of narrowing.¹³ New evidence suggests that the apparent decline in the differential in postneonatal mortality between social classes noted in the 1970s disappears when data of children born outside marriage are included in the analysis.¹⁴ A recent study, cited by Bradshaw,¹ shows that England and Wales had the highest postneonatal mortality rate of seven selected countries; only black people in the USA had a higher rate. 'Preventable' causes of infant death are three times as common in social class V compared with social class I.¹⁵

LOW BIRTH WEIGHT AND GROWTH

The low birthweight rate has not declined in line with mortality remaining at 7% for the last 20 years. The improved survival of low birthweight infants has been attributed to improvements in neonatal care. Low birth weight, still a major cause of mortality and morbidity, shows a strong social class gradient and the UK rate is high compared with other countries in western Europe.

The trend in growth towards taller children seems to have slowed in the 1980s (Department of Health, 1990, unpublished). There has been no reduction in the social class height differentials at age 20–24 between 1940 and 1980.¹⁶

MORBIDITY

The paucity of morbidity data limits comment on trends in social class differentials. The 1986 General Household Survey shows a twofold increase in long standing illness in boys (0–4 years) from families headed by unskilled manual workers compared with boys from professional families but no difference in the rates for girls.¹⁷ Children experiencing multiple hospital admissions have contributed disproportionately to the increased rate of admission to paediatric beds,¹⁸ and these children are more likely to live in deprived areas. Children admitted with significant pathology are also more likely to live in areas of deprivation (N J Spencer, B Pittapilly, S Gentle, unpublished observations).

Conflicting explanations of child health inequalities

The differing explanations of health inequalities, structural and behavioural, are well illustrated in the response of Ann Widdecombe, the junior social security minister, to the recently published *National Children's Homes' Poverty and Nutrition Survey, 1991*.¹⁹ Miss Widdecombe attributed the study findings that low income families eat

unhealthy diets and often go hungry to buying the wrong food and failing to shop where food is cheapest. The reality is far more complex. Low income families spend 30% of their income on food compared with 15% spent by high income families though, in total, high income families spend 38% more on food.²⁰ The price of 'healthy' foods has increased faster than 'unhealthy' foods, choice is restricted by access to food outlets and calorie for calorie the 'unhealthy' foods are cheaper.²¹ In addition, low income families actually spend a larger proportion of their food budget on 'healthy' foods than high income families.²²

Behaviour and 'lifestyle' are inextricably bound up with social circumstances and are themselves part of the complex mechanism by which inequalities in health develop. For the poor, 'lifestyle' choices are rarely 'free'.

Conclusions

Over the last decade the number of children living in families dependent on low income has increased sharply and families with children have taken over from pensioners as the single largest group in poverty. Income inequalities have become wider; children in lone parent and large families have been most affected by this trend.

The full effects of these changes are not yet clear. Bradshaw points to some encouraging trends in educational attainment, teenage crime, and smoking in childhood.¹ This review has concentrated on effects on health. Health inequalities persist and there is evidence for widening of social class differentials.

The ability of health services to counteract the adverse effects on children is limited. Government policy is the key to minimising the economic hardship of families with children and reversing the trend of the last decade. Essential to this is a reduction in unemployment and the elimination of low pay. Policies facilitating the combination of work and child care for mothers and enhancing the income of families with children would be positive steps.

Responsive, appropriate services for poor families are important but these families desperately need advocates. The United Nations Convention on Children's Rights and the World Health Organisation's Health For All Targets, both of which emphasise reduction of health inequalities, can be used in advocacy. Good data are essential for effective advocacy. Currently collected data and that available from carefully designed research could form the basis of an annual report on the state of children in the UK, as proposed by Bradshaw. In addition, this would ensure that statistical information available to government is brought into the public domain annually.

Paediatricians are dealing daily with the consequences of social policies that perpetuate health inequalities. It is time we 'looked upstream' and contributed actively to promoting child and family centred policies.

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Inheritance, irritants, infants, and asthma

Medicine is the study of the ways in which genetic constitution interacts with environment to produce disease. It makes sense therefore in a chronic disorder of early onset to try to observe subjects in as pristine a condition as possible in the hope of minimising the environmental contribution. Recent technical advances have made it possible to study airway reactivity in small infants and a group in Perth, Australia has looked at babies between 2 and 10 weeks of age (Sally Young and colleagues, *New England Journal of Medicine* 1991;324:1168-73).

Sixty three normal healthy babies were studied before and after histamine challenge using an inflation jacket and measuring maximal airflow at functional residual capacity (Vmax FRC). They were divided into four groups defined according to parental smoking habits and family history of asthma in first or second degree relatives. Taking F+ and F- to indicate the presence or absence of a family history of asthma, S+ to indicate that one or both parents smoked during the pregnancy and S- to indicate that neither parent smoked, the groups were: (1) F-, S- (2) F+, S- (3) F-, S+ and (4) F+ S+.

Before histamine challenge there was no statistically significant difference in Vmax FRC between the four groups of babies though it is noticeable that mean Vmax FRC was lower in those with a family history of asthma (groups 2 and 4). Airway responsiveness as measured by the lowest concentration of histamine to provoke a 40% drop in Vmax FRC was increased in groups 2, 3, and 4 compared with group 1. Thus both parental smoking and family history of asthma led to the baby having more irritable airways. There was no significant difference between groups 2, 3, and 4 in this respect and in particular group 4, in which both factors operated, did no worse than the other 2 groups.

There was a great deal of overlap between the groups as regards the measured values but it is perhaps surprising that significant differences were found at all in view of the all inclusive definition of parental smoking and the inclusion of both first and second degree relatives in the family history. It would be interesting to repeat the work looking at babies with only a first degree family history and those who parents were heavy smokers. Nevertheless the work in Perth has shown that airway reactivity occurs in very young babies and that both genetic and environmental influences appear to play a part even at this young age. The authors intend to continue their studies throughout infancy in an attempt to define more clearly the influences on airway reactivity.

Letter from Romania

Ian McKinlay

You think you have problems? A trip across the Carpathian Alps will put that in perspective. My *Hamlyn World Atlas* does have a page for the Balkans but it chops off Romania after 20 miles. Otherwise it shows the country as a small part of the eastern Europe map. *The Sunday Time Atlas* is no more informative.

Yet Romania is an ancient country—Dacia in Roman times when the locals agreed a draw with the invading legions and intermarried—hence the name. It is of similar size to the UK (just over 90 000 square miles) but has less than half of the population (now about 24 million) in spite of 22 years of Ceaucescu's promotion of fertility at all costs. These costs included huge numbers of septic abortions, a cerebral palsy incidence of about 6/1000 (but denied officially), severe overcrowding in tower block after dismal tower block in Bucharest, wholesale abandonment of children, neglect of children whose mothers had to go back to work after three months when maternity allowance ceased, and Third World levels of child and maternal morbidity and mortality.

A total of 150 000 children are said to be in institutions but this may be an underestimate as a tenth of the patients in the children's wards I visited were abandoned, some for many months. Some had their heads covered by scarves to keep the lice warm.

The state of the institutions varies from stark and smelly to cheerful but overcrowded. The staff are few, badly paid, and widely criticised. The nurses cannot afford to buy their own children the oranges, chocolates, and toys which reached the orphanages at Christmas. There is no doubt which children are worse off though.

I would not pry into the sanitary arrangements of the families of BPA members but I would be surprised if many gather for communal excretion, especially in a room with 20 others. Nor would it be normal for our handkerchiefs to be held by one individual. In the worst of the institutions, pale, apathetic children, who have never been outside, rock, roll, and eye-poke in rows of cots. It is difficult to distinguish developmentally disordered from grossly deprived children. The stench of urine and stale mash is nauseating. It reminded me of student visits to mental handicap hospitals in the UK not so long ago. The orphanage in my own authority—Swinton Industrial School, blessed by Charles Dickens and open till 50 years ago—had 1000 residents. The mental handicap hospital next door, which closed a few years ago, had hundreds more. A recent headline in our local paper demanded the closure of a

similarly foul institution for adults with chronic mental illnesses in the authority's care.

It is not just the long stay institutions which are bleak. There are children's wards in which beds are tightly crammed on the dark terrazzo floors, the walls have white tiles up to five feet and white paint above that. There are few, if any, pictures or toys or play spaces. Nurses prowl around telling children to be quiet. Parents look miserable. Boys and girls are segregated in buildings 500 yards apart. It is like Manchester 40 years ago (now, happily, transformed). Hardly any equipment is available, many drugs have become unobtainable, laboratory services are minimal, and a consultant is paid between £40-£45 per month.

As an advocate of the concept of child neuropsychiatry, I was mortified to see what was being done in the name of the specialty in some places. No wonder some public health physicians resist the development of hospital neuropsychiatry here. I understand neuropsychiatry to be the collaborative application of advanced knowledge of neurology and psychiatry for people with complex disorders relevant to both subjects. Investigation of autistic people with possible day or night seizures, understanding unusual behaviour in people with severe disabilities, and management of people who somatise their psychological distress in extreme ways were among the services the aborted Manchester child and adolescent neuropsychiatry unit planned to offer.

We had no plans to cram scores of children into a fetid concrete barracks at the back of an industrial estate in the middle of an oilfield, to deprive them of fresh air, washing machines, kitchen facilities, recreational activity, or parental visits as has been the case in Videle. We intended to allow children to wear adequate clothes even though no official visit was scheduled. It was not envisaged that children would be laid on plinths to have galvanic currents passed through their heads to make their brains grow or placed in large magnets to treat their spasticity.

Yet the neuropsychiatry department for children in Timisoara, founded in 1965, is an inspiration. It is welcoming for children and parents, it has well trained nurses, therapists with Bobath training, clinical psychologists, and a lively training programme for doctors. The department runs inpatient and outpatient services for children with epilepsy, language disorders, and other disabilities. It has community links with a polyclinic. Shortages of nurses, modern books, and journals are problems. The two main paediatric units and the

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neuropsychiatry department will join forces in a new Timisoara children's hospital soon, hopefully.

There is a delightful multidisciplinary child development centre in Bucharest with diverse wall pictures, toys, and books in every room. The team has been together for years in trying circumstances but they now work in a former sports club of the secret police.

There is a rehabilitation centre for physically disabled children in Bucharest also. Although much of the equipment is obsolete and the present building is unsuitable, parents stay with their children to learn rehabilitation techniques and a new building has been promised. The centre is the base for a newly formed association for parents and disabled people. It has just started to produce a newsletter and to arrange meetings. When the centre last received the 'red journal' it was called the *Cerebral Palsy Bulletin*, the successor to which (*Developmental Medicine and Child Neurology*) is now in its 33rd year.

The health ministry and senior management in their health service are run by practising clinicians. The minister of health is a gynaecologist, the secretary of state for health of women, children and adolescents is a paediatrician, Dr Stanescu. The director of health for Timis county (a sixth of Romania) is an orthopaedic surgeon, Dr Babusceac. All carry out their administrative work part time and also continue their clinical work and teaching.

Romanians admire the British NHS and there seems a possibility that they will set up a similar system, funded by national insurance. At present there is resistance from the finance ministry who consider the proposal a capitalist scheme, even though it has all party support in the UK where it was promoted by the Liberal and Labour parties in the early days. They are eager for contacts with British colleagues from all parts of our service and would encourage direct contact between departments. It is no longer necessary to obtain permission through their health ministry, though the ministry would welcome news of progress from time to time.

Many Romanian doctors have taught themselves English, French, and German. Though western books and journals have been unobtainable for 20 years and are now prohibitively expensive for Romanians, the basic medical training is of a high standard. Until this year the Timisoara medical school, which is a good deal older than ours in Manchester, offered two parallel courses: maternal and child health

(about 50 students per year) or adult health (about 400 students per year). Now, when the Manchester medical school is moving in the direction of undergraduate specialisation, the Timisoara courses are being merged.

There are many differences in delivery of health care from the British system. There are no general practice services but children are taken to local polyclinics for medical or other advice. Many of these resemble some of our accident and emergency departments in cities. Only now is neurology separating from psychiatry for adults. This will happen in child health services in future.

The country is potentially wealthy. It is fertile, has some oil and a petrochemical industry, a wide range of engineering experience, and a large number of humorous, talented, imaginative people, still unsure whether or not they are 'free' or what that means. For instance public swimming baths are closed at the weekends because the 'revolution' has freed people from having to work then.

The priorities are to restore the economy, to promote family planning, to reform housing policy, to establish Romanian manufacture—for example, syringes, needles, incubators, drugs—to develop strategic planning and invest in good practice rather than patch up impossible facilities. Already maternity leave has been extended to a year, the will to promote family planning is widely accepted (but materials are insufficient), contact with the international community is encouraged, and professional qualifications are being restored after seven years in which post-graduate examinations ceased and expertise was denigrated.

The friendliness, enthusiasm, and knowledge of our colleagues in Romania are a great credit to them and a potential source of benefit to us. It may be that we should consider taking some meetings there to allow Romanians to attend. Over 30 years ago western European services for disabled children began their transformation to present standards prompted by the biannual meetings of the Medical Education and Information Unit of the Spastics Society. Similar contact with a range of western European voluntary societies would help eastern countries now. We should seek every opportunity for staff exchange, scientific exchange, and investment in the future of Romanian paediatrics.

The visit to Romania was at the invitation of the Romanian Ministry of Health under the exchange agreement with the British Council in March 1991.

SISTER JOURNALS—UNITED STATES

Pediatric Research

This journal is advertised as an international journal of clinical, laboratory, and developmental investigation. It is marketed as 'Research you cannot afford to miss . . . and an offer you can't afford to pass up'. Believe you me doctor—you can. This is the journal of fetal research aimed at the physiologist. One third of the articles were about work done on laboratory animals. The journal is published in America; half the articles are from the US.

The reason why I appear to be such a philistine is not because I am antiresearch, but I don't really feel that this is a journal where discoveries of obvious clinical significance are going to be published. There is nothing wrong with the quality of the science, but the articles are very specialised and laboratory orientated and I think that 'development' is such an umbrella word that any research on newborn or young animals could be included. Inside or outside the teaching centres, unless doing an MD, how many UK clinicians are encouraged or have time to go to the laboratory or the animal house? Undoubtedly, it's our system which is at fault for the haphazard way our junior doctors are expected to publish and in most of the US academic institutions, sessions, if not months in the year are set aside for the laboratory, so this type of journal has naturally evolved. It is probably regrettable that many English paediatricians don't undertake research, don't get to the library enough, and when they

do, they head for the clinical journals and not the science. The only contact one would normally have with *Pediatric Research* would be looking up a reference and it would be unusual to come across another article of interest in the same journal.

Was there nothing in the journal of general or neonatal interest? Well—there was the article showing that term rabbits' lungs produce more superoxide dismutase in response to hyperoxia than the lungs of a premature rabbit, and this is one of the possible factors in the pathogenesis of bronchopulmonary dysplasia. That's the type of useful take home message that can be obtained by flicking through the abstracts. In general, I am concerned about the increasing tendency for research to be technological and computer orientated. Papers then have to be published validating the equipment which is used to do the research and the concept of a scientific journal of clinical importance and wide interest becomes a non-starter. Bring back the days when a problem was tackled because there was a question there to be asked and not because there was sophisticated equipment available which could be put to wider use. As for *Pediatric Research*—I'm told it's bad form to end a review saying this book/journal should be on the shelf of every departmental library so I won't say that, but somehow we should all have access to it for our occasional needs.

J G BISSENDEN

Treating recurrent epistaxis

Some 6% of 11 to 14 year olds suffer from epistaxis but the best way to manage the problem is uncertain. Basic tests of the clotting mechanism seem appropriate for any form of recurrent bleeding but how should the majority of patients who have no defect of haemostasis be managed?

Workers in Birmingham have compared the effects of cautery with silver nitrate with those of applying a cream containing chlorhexidine and neomycin (Naseptin) to both nostrils twice daily for four weeks (J Ruddy and colleagues, *International Journal of Pediatric Otorhinolaryngology* 1991;21:139–42). Twenty four children were treated in each group and there was no significant difference as regards recurrence of epistaxis between the two groups after eight weeks. Cautery was a painful procedure despite the use of a local anaesthetic.

Unfortunately the lessons to be learned from this trial are limited. There was no untreated group so we don't know whether either treatment was effective. If the antiseptic cream is effective it is unclear whether the antibacterial components are important or whether any cream would do. The authors suggest using the antiseptic cream as first line treatment but to my mind they have shown that more work is needed.

ARCHIVIST

LETTERS TO THE EDITOR

Gut blood flow velocities in the newborn: effects of patent ductus arteriosus and parenteral indomethacin

SIR,—Skinner *et al*¹ seem to suggest that the rapid fall in blood flow velocity seen in the cerebral,² renal,³ and mesenteric,⁴ arteries after an intravenous bolus of indomethacin is due to rapid closure of the ductus arteriosus and a simultaneous fall in cardiac output. Is their explanation for the recovery of regional blood flow velocities after the acute fall a gradual reopening of the ductus with increasing output?

There are several reasons why we believe the rapid fall in mesenteric blood flow velocity reflects a regional vasoconstriction rather than a fall in cardiac output. Our data indicate clearly that the coeliac axis and superior mesenteric artery do not behave in the same way, a reflection of the very different vascular beds which they supply. The fall in peak systolic velocity in the coeliac axis was significantly less than in the superior mesenteric artery ($p < 0.034$). Moreover, our child with Fallot's tetralogy, who did not have retrograde diastolic flow and was inadvertently treated with indomethacin, showed no change in clinical state, yet showed the expected fall in coeliac and superior mesenteric artery blood flow velocity.

Bolus indomethacin results in a rapid increase in systolic blood pressure which parallels the changes in regional blood flow velocity representing, we believe, considerable peripheral vasoconstriction.^{3,5} This is hard to equate with the suggestion of Skinner *et al* of a rapid fall in cardiac output, especially when data from Saliba *et al* demonstrate very clearly that ligation, as opposed to the treatment of the ductus with indomethacin, does not affect systolic blood pressure, but does produce a rapid increase in diastolic blood pressure and immediate return of forward diastolic flow velocities.⁶

There is no doubt that indomethacin does affect the ductus and that left ventricular output decreases with ductal closure. The question, however, is how to interpret the observed changes in regional blood flow velocity. We would suggest that ductal closure is represented by the return of forward end diastolic flow velocities which appears to be a good predictor of eventual ductal closure and that the rapid fall in velocity represents a local vasoconstriction which can be avoided by the slow administration of indomethacin which is equally effective at closing the ductus.

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Changes in body composition and energy expenditure after six weeks' growth hormone treatment

SIR,—It was gratifying to read the well controlled study by Dr Gregory and colleagues, documenting impressive changes in body composition and energy expenditure after only six weeks of treatment with biosynthetic growth hormone (hGH).¹ Nicolaidis and Even in 1986 introduced the term 'leptogenic' (from the Greek word leptos=lean) to describe pharmacological agents that reduce body fat by the following means: (i) affecting appetite/satiety mechanism, (ii) altering metabolism, (iii) adjusting set point controls, and (iv) through other peripheral/central nervous system effects. Research by ourselves and others (Ritzen from Karolinska Institute, Stockholm, Klish and colleagues from the Baylor College of Medicine, Houston, and Saenger and colleagues from Albert Einstein College of Medicine in the Bronx, New York) presented at the International Congress on Prader-Willi syndrome in the Netherlands in May, 1991, has documented that changes in body stature associated with the administration of growth hormone to children with Prader-Willi syndrome are often accompanied by reductions in percentage of body fat. In light of the observation reported by Forbes that children with Prader-Willi syndrome show strikingly less lean body mass than equally overweight children with exogenous obesity² and the demonstrations by Hill *et al*³ and Schoeller *et al*⁴ that energy expenditure is also considerably reduced in Prader-Willi syndrome, the findings by Gregory *et al* suggest that hGH exerts its leptogenic effects by increasing the metabolic activity of the fat free mass.

Analysing the cases reported by Gregory *et al* that showed a decrease in resting energy expenditure expressed as a percentage of total fat free mass suggests that additional research might be helpful in predicting who might show a leptogenic effect to hGH treatment. Responders had normal variant short stature or isolated growth hormone deficiency. Children with acute lymphoblastic leukaemia or craniopharyngioma showed reduced metabolic activity.

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Indwelling cannula for insulin administration in diabetes mellitus

SIR,—I read with interest the study on the use of indwelling cannulas for insulin administration¹ and would like to report different experiences with the same device in diabetic subjects.

During summer camps in Austria in 1989, 49 diabetic subjects (aged 9-22 years) used the indwelling cannula (Insufion, Viggo) in an open trial to test the acceptance of this device in those who inject themselves. The proposed indwelling time was 144 hours for each cannula. All the subjects were used to giving their injections themselves, most had two daily insulin doses, and about a quarter used insulin pens for multiple injections. The first insertion of the cannula was done by a doctor, afterwards the subjects were allowed to insert it themselves under supervision. The skin was carefully dried before insertion; insertion sites were the abdominal wall or thigh.

Fifteen subjects used the cannula only once, 13 twice, 15 three times, five four times, and one six times. The mean indwelling time was only 41.5 hours (range 1-120 hours), which is much shorter than in the British¹ or Swedish study.² Reasons for removal or change of the cannula were: loss during sports (21.4%), spontaneous loss (21.6%), pain at the insertion site dependent of injection (14.2%), and local inflammation (10.7%). In 34 cases a bacteriological culture of the cannula insertion point was performed and in 15 (44.1%) *Staphylococcus epidermidis* was found. No obvious changes in metabolic control could be observed during the use of the indwelling cannula. After the summer camp only four subjects (8.2%) wanted to continue to use the device.

Because of the failure of the adhesive patch the indwelling time in these subjects was only 35% of the proposed time. Therefore the major advantage of the device in reducing the number of injections was lost. Whether the Austrian climate, with higher average summer temperatures and increased sweating during normal sports, contributes to the high percentage of spontaneous losses is unclear. It is interesting, however, that the studies reporting longer indwelling times for the cannulas came from northern Europe.^{1,2}

In conclusion, it is my opinion that an indwelling cannula (at least in the available form) is of no advantage compared with conventional injections. Relatively high costs and the possibly increased risk of local infections must also be taken into account.

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Professor Hughes and Dr Long comment:

We were interested to read of Dr Schober's experience of using the Insuflon cannula in 49 young diabetics. The circumstances in which he used the device were entirely different to those operating during our study. The comparison is therefore not a valid one other than to comment that the device did not appear to be either effective or acceptable when tried out in a summer diabetic camp setting. We did have problems ourselves until we learned how to apply consistently the adhesive patch, such that our diabetic children were then able to participate in a wide range of activities.

We re-emphasise the value of this type of indwelling cannula device for the administration of insulin to newly diagnosed diabetics and for those children with needle phobia. Clearly, further studies are required to determine whether such a device would be of practical benefit in a wider range of circumstances.

$\gamma\delta$ T cells in human breast milk

SIR,—We previously reported that the proportion of lymphocytes bearing the $\gamma\delta$ T cell receptor is significantly higher in human colostrum than in either autologous or heterologous blood samples.¹ Additional studies revealed that the great majority of colostral $\gamma\delta$ T cells react with a monoclonal antibody (δ TCS1) which recognises actively motile cells that express non-covalently bound $\gamma\delta$ chains.² To characterise further the phenotype of this small, but numerically important, T cell subset, we have now examined eight milk lymphocyte suspensions with a more complete panel of monoclonal antibodies directed against T cell related antigens.

Direct and indirect immunofluorescence staining techniques followed by two colour cytofluorimetric analysis showed that only a few (15-35%) milk $\gamma\delta$ T cells (TCR $\delta 1^+$) were CD8⁺, whereas nearly all were CD4⁺, CD5⁺, and CD7⁺. In contrast, an overwhelming preponderance (85-95%) of colostral $\gamma\delta$ T cells displayed the HML-1⁺ phenotype. This is the reverse of situation encountered in the bloodstream, where HML-1⁺ T lymphocytes are virtually absent.

Although the origin of colostral T cells is still a matter of conjecture, the fact that the phenotypic pattern of milk $\gamma\delta$ T lymphocytes is similar, if not identical, to that of the intestinal intraepithelial counterpart³ suggests that these cells might originate in the gut associated lymphoid system and home to the mammary gland late in pregnancy and throughout lactation. This selective homing process by immune system cells has been well documented in experimental animal models.⁴

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Segmental colonic transit time in Duchenne muscular dystrophy

SIR,—We read with interest the recent paper by Korman *et al* concerning the oro-caecal transit time in Duchenne muscular dystrophy.¹ In contrast to reports of gastric hypomotility and intestinal pseudo-obstruction, the authors found a normal oro-caecal transit time. Therefore the genesis of patient's constipation is not due to impaired small bowel motility. Colonic motility had not yet been studied in Duchenne muscular dystrophy.

For this reason, we recently studied segmental colonic transit time in 12 patients, aged 8 to 18 years (mean 12.3 years). Eight of them were confined to a wheelchair. Gastro-intestinal symptoms were noted and segmental colonic transit time was performed according to a method previously described²: 20 markers were given at breakfast time to the patients for three consecutive days and plain film of the abdomen was taken at the fourth and seventh days.

Ten children had at least one criteria of constipation: less than three stools per week ($n=5$), difficulties in defecation ($n=7$), and hard stools ($n=3$). Ten had gastrointestinal symptoms: abdominal pain ($n=7$) proctologic abnormalities ($n=5$), encopresis ($n=2$), and abdominal distension ($n=2$). Results of segmental colonic transit time are reported in the table. Seven of 12 children with Duchenne muscular dystrophy had an abnormal colonic transit time: three had stagnation of markers in the rectosigmoid area and four had an abnormal transit time in all the colonic segments. No relationship was found between colonic transit time and either gastrointestinal manifestations or gravity of muscular dystrophy.

Our results show that impairment of colonic transit time is frequent in Duchenne muscular dystrophy. Immobility, weakness of abdominal wall muscles and smooth muscle involvement

of the colon⁴ might explain the high frequency of constipation in these patients.

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Surfactant treatment for premature babies—a review of clinical trials

SIR,—In the review article on surfactant treatment,¹ Surfactant (Abbott Laboratories) is described as a frozen aqueous suspension. The current formulation of Surfactant, recently approved for commercial use in the United States, is a suspension requiring refrigeration only. Before administration, Surfactant vials are warmed to room temperature.

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Paediatric Laboratory Medicine Fund of the Royal College of Pathologists

SIR,—Funds have been made available to promote scientific interchange in all branches of paediatric laboratory medicine in the UK.

Segmental colonic transit time in 12 patients with Duchenne muscular dystrophy

Age (years)	Right colon* (hours)	Left colon* (hours)	Rectosigmoid* (hours)	Total* (hours)	Constipation	Other gastro-intestinal symptoms
8	6	1	13	20	+	+
9-5	2	1	41	44	—	+
10	30	35	10	75	+	+
11	14	6	8	28	+	+
11	2	1	28	31	+	+
12	24	20	41	85	—	+
13	12	14	47	73	+	—
14	1	11	29	41	—	+
14	13	1	41	55	+	—
15-5	59	61	0	120	+	+
16	4	4	30	38	+	+
18	50	37	7	94	+	+

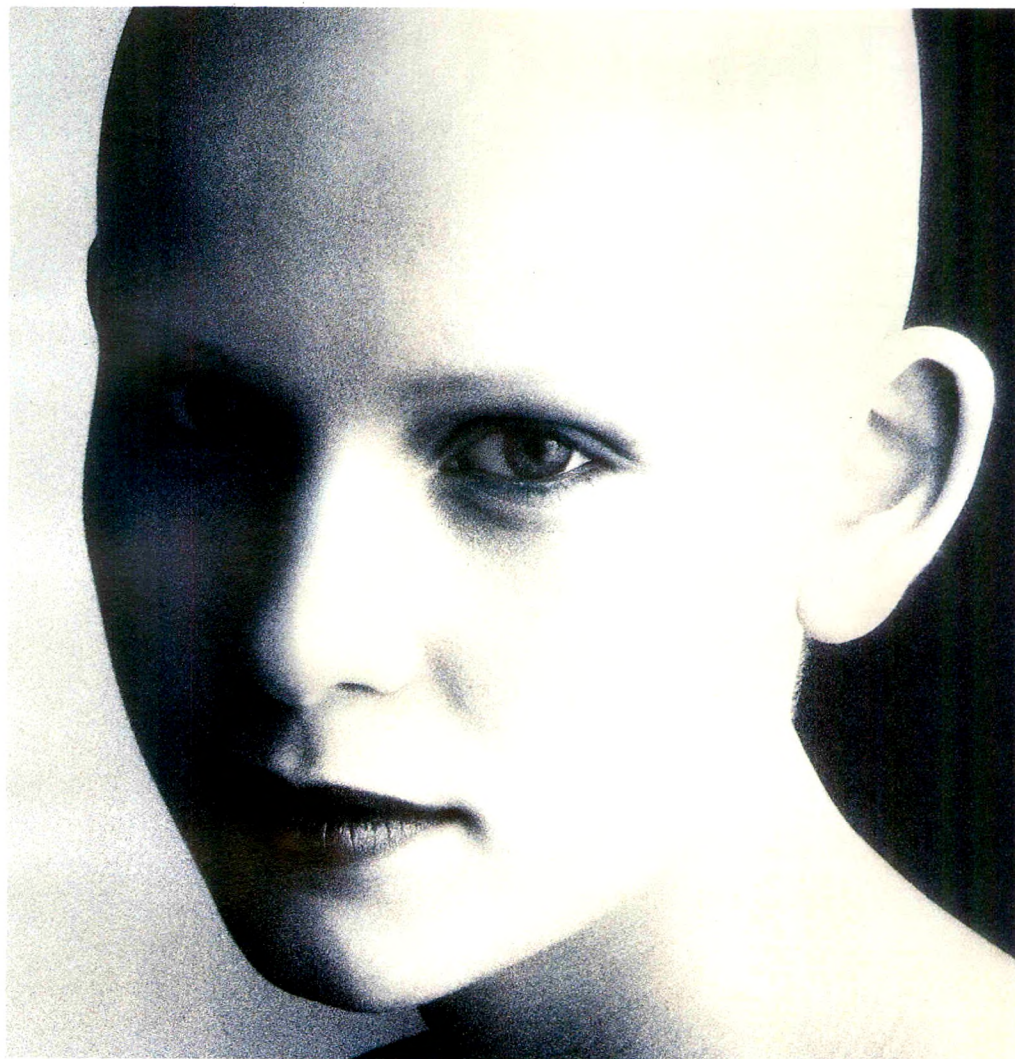
*Upper limits of normal range of colonic transit time in French children are right colon, ≤ 18 hours; left colon, ≤ 20 hours; rectosigmoid, ≤ 34 hours; and total, ≤ 62 hours.³

Abnormal values underlined.

Plus (+) and (—) signs indicate present or absent.

HML-1 monoclonal antibody was kindly supplied by Dr N Cerf-Bensussan, INSERM U132, Hôpital des Enfants Malades, Paris, France.

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The fund is administered by a committee which is chaired by Professor Dame Barbara Clayton. Applications for grants for the following purposes will be considered: (1) to help laboratory workers to attend meetings in the UK or abroad. (2) To support the travel of laboratory workers to recognised institutions to learn techniques. For the latter purpose priority would be given to applications from junior workers. (3) To support meetings on paediatric laboratory medicine in the UK. The support could be: (a) a contribution to a meeting on paediatric laboratory medicine or (b) sponsorship of a special lecture or session relevant to paediatric medicine organised as part of a larger meeting.

For further details and application form please write to me, Fund Secretary, at the address shown below.

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atlantic I leave to their whim. Secondly, now that many postparturients stay in hospital for so little time a pocket neonatal paperback is vital. Thirdly, a work that details useful practice in screening and surveillance which, I should point out, will pay for itself many times over—financially as well as sapientially. Finally, and this is the one I will breathlessly tell Sue Lawley will accompany me to my island retreat, no-one should practice children's medicine without a copy of the late Ronald Illingworth's *Common Symptoms of Disease in Childhood*.

HARVEY MARCOVITCH
Consultant paediatrician

Recent Advances in Paediatrics 9. Edited by T J David. (Pp 256; £19.95 softback.) Churchill Livingstone, 1990. ISBN 0-443-04304-3.

For practical purposes medical knowledge is now infinite and has a half life of about a decade. The central dilemma for its disciples, therefore, especially in as wide a discipline as paediatrics, is to keep abreast of the knowledge they need. Many scan the periodicals with remarkable diligence but much of their content is merely the gossip of medical science and shrinks to invisibility when the necessary correction factor for contemporary research is applied. Others have faith in the electronic revolution and can absorb only preprocessed byte sized morsels but these will remain digestible only to addicts until our race evolves a serial or parallel port. The best medium for conveying knowledge and stimulating thought is the short essay reviewing a topic on which the author has thought long and hard and has sifted and organised the knowledge available. A collection of such essays should be well printed, light enough for the lap, cheap enough for the pocket, and enclosed in a fluid resistant cover. This volume meets these preliminary criteria, so what of the contents?

There are 12 essays covering bacterial meningitis, primary immunodeficiency, constipation, short stature, diabetes mellitus, developments in ear, nose, and throat surgery, infants of drug dependent mothers, the thermal environment of sleeping babies, the symptoms and signs of illness in infants, respiratory distress syndrome, support after sudden infant death, and cows' milk allergy. In a final chapter, the editor adds a brief telegraphic review of the paediatric literature of 1989.

This is a good selection, including six general paediatric and six neonatal/infantile topics and apparently working on the principle of something old, something new, but nothing blue. It is a relief to be given respite from consideration of deliberate abuse of children but there are more surprising omissions. *Nothing* on genetics?! It seems at first the biological revolution has been completely ignored but, turning to the index with bated breath, there is a single reference to DNA probes.

Reflecting the principles stated above, those essays that review and update an important topic are most enjoyable and instructive. Most of these have been reviewed many times before, often by the same authors, and there is a risk of battle fatigue when old and tried warhorses are wheeled into the front line yet again. However, a discerning editor such as Dr David can judge who is not yet due for the knacker's yard. An exemplary chapter is that

by Levin and Heyderman on bacterial meningitis, in which old knowledge is consolidated and recent advances are critically appraised in the space of 19 pages. The essays on recent work are also valuable but are likely to need substantial revision in subsequent volumes. The terminal literature review seems too personal and already too dated to justify a place in such a collection.

This volume is a worthy successor in a distinguished line. Annual publication is now planned and will be warmly welcomed if such a high standard can be maintained. Paediatricians should buy the book and make time to enjoy it a chapter at a time, but beware the advice of John Dryden to '... make a short essay, then hasten to get drunk, the business of the day'.

NICK BARNES
Consultant paediatrician

Constipation in Childhood. By Graham Clayden and Ulfar Agnarsson. (Pp 123; £9.50 paperback.) Oxford University Press, 1991. ISBN 0-19-262027-4.

Despite all the recent advances in the management of childhood disorders, constipation remains very much part of the bread and butter of paediatrics, both in general practice and the hospital setting. Unfortunately, it is often inadequately or poorly treated with resultant distress for the child and family.

The aim of this book is to assist paediatricians, family doctors, and others involved in the management of children with constipation. The book starts by going into the anatomy of the anorectum and physiology of anal continence and defaecation, thus providing a scientific basis for the management strategies of constipation. This is followed by a discussion of constipation in babies, toddlers, and older children and the special problems of children with disabilities.

Most children with constipation do not require extensive investigations and therefore, quite appropriately, the chapter on the medical management of constipation precedes that on investigations. Surgical treatments are briefly discussed followed by a chapter on psychological management. The final section of the book consists of a booklet designed to be photocopied and given to parents and children.

The practical and logical approach to constipation set out by the authors should make this book compulsory reading for anybody involved in the management of constipation in childhood. It is relevant to health visitors and general practitioners, as well as paediatricians. Added attractions are the parents' booklet and the very reasonably price of this book. I would recommend that every paediatrician and general practitioner should purchase this book.

A W BOON
Consultant paediatrician

The Multi-Professional Handbook of Child Sexual Abuse. By Tilman Furniss. (Pp 357; £20 paperback.) Routledge, 1991. ISBN 0-415-05563-6.

Begin this book at the beginning. Start with the introduction where Professor Furniss warns of part 1, it 'may be difficult and dry reading'. He advises the reader to look up

AUTUMN BOOKS

Whenever I read a book review I am reminded of my guilty secret: as a clinical student I spent not a penny on textbooks, excluding the 7/6d demanded by my medical school library to replace a copy of *Aids to Anatomy* stolen by an expectant, but doubtless disappointed, burglar.

My guilt is not because I am afraid I might be ill informed but because authors deserve better than to have their work unrecognised. The only way to assuage it is to persuade others to read while begging and borrowing cash to replenish the ward library. There is no longer any time to wade personally through a textbook, unless it be about resource initiatives or contracting; it may not even be necessary to read these if you borrow your infant child's copy of Andersen's *The Emperor's New Clothes*.

Those whom I most frequently try to persuade are the senior house officers. All of mine are expected to become general practitioners. It has long been a custom of that trade to demand assessments of its trainees which are in strict non-confidence. Many of us find it awkward to criticise in print a senior house officer who will remain working with us for several months. After a time I become ashamed of my own euphemisms but at least there is one area where criticism can be unbounded. One of the standard assessment questions refers to the trainees' reading habits. One cannot know what goes on in the privacy of their hospital cells between bleep calls but I doubt if much serious reading goes on except in preparation for diploma exams.

Before they leave for the outside world I suggest four books in which they should invest personally. Firstly, a large multi-author textbook to keep at the phoneside so that as general practitioners they can be one step ahead of their patients or as registrars, of their house officers. Whether homegrown or trans-

practical problems in part 2 and be lead back to the theoretical, part 1. This is good advice as the practical advice, for example, 'preparation for disclosure' is easily accessible and with this in mind the reader can more easily tackle part 1.

Professionals in the wake of Cleveland, Rochdale, Orkney, and where ever next, need a conceptual framework in which to practice, as with a greater understanding of the child, his family, the professionals and their networks, practice should develop to allow avoidance of some of the problems of the past.

One of this book's strengths is the clear insight it gives into why interprofessional work is so difficult. The section on professional networks and interprofessional problems should be obligatory reading for all doctors. Mirroring processes, conflict by proxy, and conflict between medical and legal systems are well described.

Professor Furniss well understands the professionals attempting to protect children falling back exhausted, joining in the collusion and denial of abuse. How would he tackle the apparent recent raising of the legal hurdles as the level of proof required by care courts increases?

An early revision of this book is indicated. The presence of parents and teenagers at case conferences is a new challenge. How to treat young abusers—25% of perpetrators in our Leeds study are in mid-childhood through adolescence. Female abusers are being increasingly recognised. The Children Act is upon us.

All paediatricians who work with children who have been sexually abused will find this book useful. The paperback edition is cheap, the format clear, and the index adequate. The references are few and dated but this is acceptable given this is essentially a handbook of professional management based on clinical experience.

I would suggest colleagues buy this book and dip into it, it is well worth the effort.

JANE M WYNNE
Consultant community paediatrician

Multiple Congenital Anomalies. Edited by Robin M Winter and Michael Baraitser. (Pp 1433; £175 hardback.) Chapman and Hall, 1991. ISBN 0-412-29130-4.

This huge text, 3.8 kg on my kitchen scales, and 8 cm thick is the offspring of the London Dysmorphology Database, which has become an indispensable tool for dysmorphologists around the world. While the contents of the book and the database are much the same, they complement rather than rival each other, as they both have a role in different situations. In addition there are some diehards who will always prefer a book to a computer in any situation.

This book is just what the authors call it, a diagnostic compendium. It is not an illustrated textbook, rather a comprehensive gazetteer of multiple congenital anomaly syndromes, of which there are now over 2000 described. Part 1, printed on delicate blue, comprises about 4 cm of the depth and is an alphabetical listing of syndromes. For each disorder, the inheritance pattern where known is given, then an abstract of about one paragraph describing the disorder followed by a listing of features. Each entry ends with a comprehensive reference list with some as recent as 1990.

The second major part of the book (in pink) is a diagnostic index where a single feature forms a main heading, followed by groups of additional features which are found with the main feature in certain disorders. The user having identified a possible match for their patient can then look further in the blue section for details and references. There are three small appendices listing the features used in the diagnostic index, features not used either because they are so common or non-specific, and a list of syndromes with synonyms.

I believe that this book is a useful addition to the diagnostic tools available for dysmorphologists and paediatricians, particularly neonatologists and developmental specialists. Its disadvantages are that for it to be fully used access to a well stocked library is necessary; it also lacks photographs. Its great strengths are its ease of use and the comprehensive reference lists. The compendium's main use is as a diagnostic aid but an important secondary use is an aid for preparation of publications. I would strongly recommend that a copy be available in departments where it will be well used by those in training, as well as by the more senior members.

DIAN DONNAI
Consultant clinical geneticist

Paediatric Neurology. 2nd Ed. Edited by Edward M Brett. (Pp 912; £90 hardback.) Churchill Livingstone, 1990. ISBN 0-443-03788-4.

The gourmet may dip in to the *Good Food Guide* and the architect may clutch Pevsner's *Buildings of England*. There are medical texts of similar stature and I think Edward Brett's *Paediatric Neurology* is one of them.

The first edition is already a standard work. This second edition was needed to cover recent advances and to fill 'lacunae' in the first. The book maintains its unique and stimulating voice because Dr Brett is author or coauthor of the majority of its 27 chapters. He draws on extensive clinical experience and wide knowledge of the literature. He writes with humanity and wit.

An example of the clinical experience displayed throughout is found in the section on eye movement disorders. Cogan's oculomotor apraxia is described. This is rare but we are told that it is sometimes found in those classed as 'clumsy boys' and a rather similar defect is seen in ataxia-telangiectasia, Huntingdon's chorea, Wilson's disease, and Niemann-Pick type C disease. We need a writer of Dr Brett's experience to discuss such difficult topics. Not that the book only deals with rarities: there are chapters on cerebral palsy and migraine, for instance.

There are many examples of the author's humanity and wit. I was interested to read that spectacles can be invaluable tools for assessing motor coordination when being snatched from Dr Brett's nose and I was amused by the illustration of the 'Bugs Bunny personalised patella hammer'. I was impressed by a sensitive discussion of the parents' dilemma when faced with the task of telling their son that he has Duchenne muscular dystrophy.

The coauthors are experts in their fields and they maintain the high standard. They help to cover every aspect of child neurology from autism to ataxia and from xeroderma pigmentosum to X linked mental retardation. 'Bedside' experience is supplemented by

chapters on neurophysiology and neuroradiology.

I am sure that paediatric neurologists will want to consult this book and I hope that adult neurologists will read it. However, its appeal is more widespread than that. Every medical library should have a copy and I strongly recommend it to hospital and community paediatricians.

In the preface to the first edition Dr Brett wrote that in order to practice paediatric neurology 'head and heart are both required'. It is clear that he has used both head and heart in writing this book.

C M VERITY
Consultant paediatric neurologist

Paediatric Epilepsy. Edited by M Sillanpaa, SI Johannessen, G Blennow, and M Dam. (Pp 377; £45 hardback.) Blackwell Scientific Publications, 1990. ISBN 1-871816-07-6.

In the middle of the journey of my life,
I came to myself in a dark wood
where the straight way was lost.
Dante: *La Divina Commedia*

The quotation is used by Anders Munthe-Kaas describing the experience of parents when first learning of the diagnosis of epilepsy in their child. It may well be an apt description of the experience of many general paediatricians when faced with the diagnostic and management difficulties they encounter with some of their epileptic patients. Through its collection of 37 chapters written by a variety of Scandinavian and American contributors the way is illuminated most effectively.

The editors intend the book to be read by paediatric neurologists, general paediatricians, and general practitioners. They have succeeded in their task. Each chapter starts with an introduction and definitions where needed and ends with broad conclusions or summary. For the generalist this is helpful particularly in the chapters on standard diagnostic investigations and the more research oriented tools of single photon and positron emission computed tomography (SPECT and PET). These chapters discuss clearly the indications and limitations of the procedures.

Overall the chapters are logically arranged. Early chapters deal with epidemiology, neuropathology, and classification followed by chapters on each of the commoner epileptic syndromes. British readers may find the Scandinavian perspective on incidence and prevalence limiting, although it is placed in the context of the 1975 Hauser and Kurland study from Minnesota. The chapters on individual syndromes are clear with up to date reviews. Tuchman and Moshe draw attention to an important distinction between seizures and movement disorders in the neonate with advice on possibly unnecessary prescribing of anticonvulsant therapy.

The later chapters deal with drug treatment, side effects, and monitoring. The tables listing the pharmacokinetic properties and indicated antiepileptic drugs for different seizure types are clear and informative. Of the new anticonvulsants there is some mention of oxcarbazepine but it was disappointing not to see more information about vigabatrin. Gram discusses critically the rationale behind drug dosing and monitoring, emphasising the importance of rapid determination of drug

concentrations within the clinic setting using commercial kits.

We submit probably too few patients with intractable epilepsy to surgery (Loyning). The results of the Norwegian and American experiences have been surprisingly encouraging. It is probably the paucity of centres with experience in selection procedures that has limited the numbers over the years. Alternative approaches to managing epilepsy along behavioural lines are explored by Dahl with a critical review of research in the area. The closing chapters deal with prognosis and habilitation of the child within the family and community. The latter is detailed in a series of chapters describing the experiences of different Scandinavian countries.

In conclusion, this collection of chapters on paediatric epilepsy provides a very readable and up to date review on the current state of the art. Although its price and the somewhat Scandinavian perspective may discourage individual purchase, there is little doubt that it would be an invaluable addition to any general paediatric library.

R M BUCHDAHL
Consultant paediatrician

Mixed Blessings: Intensive Care for Newborns. By Lynda Lytle Holmstrom and Jeanne Harley Guillemin. (Pp 317; £13.50 paperback.) Oxford University Press, 1990. ISBN 0-19-506659-6.

I believe the book has been written by two sociologists but no reference in the introduction to their profession is perhaps deliberate to keep the reader unbiased. It is all about the interprofessional relationships in a level III neonatal intensive care unit in the USA. The authors spent a lengthy period at one particular unit in America and then visited other countries including the UK, but there describing only the organisation of perinatal care. The book is really aimed at the American market and some of the situations could only happen in the USA. However, there is something of interest for all in neonatal intensive care units in any country. If I were going to list the professionals who would get most out of the book they would be psychologists, social workers, managers, nurses, and then doctors in that order.

I loved the dialogue. A compilation of quotes from various parts of the book could be as follows:

Resident at morning round: 'Last night I transported a preemie of 600 g who seized [convulsed] all the way. He arrested on arrival so I retubed [reintubated] him. He was really crumping [deteriorating] all night but didn't have the decency to check out [die]. If he makes it, he'll probably be a gork [severely retarded]'.

Fellow: 'Does this kid have a murmur?'

First resident: 'Intermittently. . .'

Second resident: 'I don't think so'.

Third resident: 'Me neither'.

Nurse: 'I do. I've heard it'.

Fellow: (sarcastically): 'Then yes it is!'

Mixed Blessings deals with referral to the neonatal intensive care unit, the running of that unit, and the ethical problems created. It describes with great insight the positive and negative relationships of all who work together and the behind the back gossiping and the heart rending antburn out open sessions orchestrated by the unit psychiatrist. The

good guys are the nurses, the bad guys are the doctors, and the really bad guys are the directors of the units who are out of touch and appearing only for the grand rounds. UK readers will smile at the thought of social worker rounds—not because it is a bad idea but because social workers are like gold dust. When present in great supply as in the unit described in the book, only the nurses attended the rounds which were boycotted by the doctors.

Although criticism is levelled at the inconsistency of ethical decision making, the authors present no better solutions. The book is not an exercise in philosophy but more a commentary on what actually happens. If one remembers that these are the views of outsiders looking at the drama of neonatal intensive care which we take for granted, then the merits of the book come through. On my unit, I see it a helpful book for nursing projects on organisation, staffing, or ethics. Doctors will mainly have a good laugh but that's how the book describes us and I wouldn't want to ruin our image.

J G BISSENDEN
Consultant paediatrician

Kendig's Disorders of the Respiratory Tract in Children. 5th Ed. Edited by Victor Chernick. (£130.50 hardback.) W B Saunders Company, 1990. ISBN 0-7216-2214-3.

This new edition comes only seven years after the last and perhaps illustrates the growing importance of paediatric respiratory medicine in North America. It is a large multiauthor textbook with mainly North American contributors. It has a reputation of being a 'bible' of paediatric respiratory medicine and this edition will help to maintain its place as an important reference book.

Although only 50 pages longer than its predecessor, it does weigh almost 1 kg more! It covers all aspects of paediatric chest medicine from neonatal disorders to the rare and esoteric. There are seven new chapters which include up to date information on infant lung function, exercise testing in children, sleep disorders, and chest problems in paediatric AIDS, all of which are useful additions. The chapter on chest problems in paediatric AIDS is particularly good. Many chapters have been updated and are excellent, including those on sudden infant death syndrome, a large section on respiratory infections, and the chapter on cystic fibrosis. However, some sections are disappointing. The chapter on asthma, although strong on pathophysiology, is weak on clinical management. It tends to portray American views on management with little mention of either sodium cromoglycate or inhaled steroids.

In general the accounts of physiology and pathophysiology are very good. Any multi-author book of this size will contain omissions, but it is still a very helpful reference book for paediatricians with an interest in respiratory medicine, as well as for juniors in training in this subspecialty. However, I would not recommend it for medical students, or for doctors who do not have a particular interest or knowledge of paediatric respiratory medicine. There are smaller and cheaper books available!

P H WELLER
Consultant paediatrician

Basic Mechanisms of Pediatric Respiratory Disease: Cellular and Integrative. Edited by Victor Chernick and Robert B Mellins. (Pp 449; £69.50 hardback.) B C Decker Inc, 1991. ISBN 1-55664-137-0.

As stated in the preface, this book has been produced to bring together current knowledge on the cellular and molecular biology of the lung, together with up to date information on the anatomical and physiological development of the respiratory system and how this can be affected by pathological processes. There is an initial statement on contribution of DNA technology to our understanding of lung disorders, followed by a very clear section on the factors controlling the development and repair of the lung at cellular level. The remainder of this second section is on the prenatal and postnatal development of the lung and the pulmonary circulation and how these processes can be disturbed by cardiopulmonary disorders. The third and largest is on the developmental physiology of the lung including the development of upper airway reflexes and laryngeal function, lung mechanics in the developing infant, and what is currently known about the transfer and transport of oxygen and carbon dioxide, fluid, and electrolytes in the lung. The remainder of this section is concerned with respiratory control before and after birth, cardiorespiratory interactions, neural control of the lung, bronchial reactivity, and exercise. The fourth section on developmental biochemistry is concerned largely with the surfactant system in the newborn, and also a very good reference section on oxidants and antioxidants and airway sections. The next section is concerned with the development of pulmonary defence mechanisms including inflammation and mucus clearance, and the remaining 50 pages on lung imaging, nuclear medicine, aerosol treatment, and current concepts in high frequency and jet ventilation.

This book is likely to have a fairly restricted readership, but will prove invaluable to anyone with a significant interest in the respiratory system, particularly those about to commence research related to the growth, development, or physiology of the lung. I personally found this one of the most exciting books that I have come across for a long time. It should certainly be held by all the major medical libraries in the country, and even at the relatively high price of £69.50, represents excellent value.

A D MILNER
Professor of paediatrics

Tumors of the Newborn and Infant. By Hart Isaacs Jr. (Pp 251; £53.50 hardback.) Mosby Year Book, 1991. ISBN 0-8151-4809-0.

Tumours provide a supreme example of the way that specific disorders may be linked to particular periods of development. In the newborn infant neuroblastoma and teratomas are the most frequent forms of tumour, leukaemia is the major fatal tumour, and malignant tumours of the kidney are almost unheard of. Within the first year of life the whole range of paediatric tumours may become manifest including three different varieties of malignant renal tumour alone.

This changing pattern of developmental tumours with age provides ample justification for Hart Isaac's new monograph dealing specifically with tumours seen in the newborn or infant. Initial chapters on aetiological

factors, incidence, mortality, and diagnosis are followed by a series of brief but extremely well referenced chapters on individual tumour types and tumours of specific tissues or organs, for examples, neuroblastoma, germ cell tumours, and renal tumours. The book is intended mainly for pathologists and handles the problems of classification and macroscopic and histological diagnosis in considerably more detail than those of treatment. For the latter purpose the reader is often referred to other works on paediatric oncology.

The work is very readable and in general up to date, providing an excellent review of the subject. An occasional failing is recognisable. Thus while quoting reports of the occurrence of primitive neuroectodermal tumours in macerated fetuses the author omits to mention more recent evidence that such 'tumours' are usually artefactual. A major criticism is the small size and poor quality of most of the illustrations, some of them being uninterpretable and detracting from, rather than enhancing, the value of the text. A linked problem is the use of a different and, for this aging reviewer, less legible typeface for the legends than for the text. Despite these visual drawbacks the book can be thoroughly recommended as a useful work of reference to pathologists concerned with the diagnosis of paediatric tumours and also merits consultation by paediatricians and paediatric surgeons.

J S WIGGLESWORTH
Professor of perinatal pathology

Living with Haemophilia. 3rd Ed. By Peter Jones. (Pp 256; £19 hardback.) Castle House Publications Ltd, 1990. ISBN 0-7194-0152-6.

The best thing the old General Nursing Council did was to put a question in the final nursing examinations about haemophilia. Since then, nurses regularly attend the Haemophilia Centre for training in hospital and home care, and the whole hospital seems more aware of the disease and its problems. Dr Jones' book is written for the haemophiliac and his family, and describes all they need to know and more about the haemophilias. It should similarly raise awareness about the disease for the layman. This is the third edition. It is comprehensive and comprehensible. The details are written in terms which all can understand and the diagrams are clear and simple. The popularity of earlier editions can be judged by the fact they have been published in six other languages. Over the years I have forgotten how many copies my department has bought to lend to patients, but they are numerous. Once they go, they rarely come back.

How does this differ from earlier editions? The book is now printed with more words to the page so is more informative but only slightly larger. A new first chapter reassures the parents of a newly diagnosed child. The statement that 'he has as much chance of being captain of one of his country's sports teams as his father' may be taken two ways. Other new chapters include information on side effects of treatment such as liver disease and infection, HIV and AIDS, and on haemophilia care in developing countries, and vaccination schedules including hepatitis B. There are many new diagrams and increased information about contraception, factors VIII and IX, von Willebrand's disease, hepatitis, and antenatal diagnosis. Another innovation is the inclusion of photographs of haemophilic boys enjoying a range of physical activities, despite some

obviously bad knees and legs. These are all improvements.

My own experience tells me that the earlier editions served their purpose well, and I have no doubt that this edition will do the same. Its message, as the author states, is 'life first, haemophilia second'. However, in his attempt to reduce the anxieties of parents newly faced with a diagnosis of haemophilia, the author plays down the severity of the disease. For many patients, even with first class management, the disease presents major problems for their enjoyment of life, their ability to work and play, and their prospects. Even so, all families of a child with haemophilia should read and study it. If they do, they will know more about the disease than their paediatricians. This reversal of roles is bad for medical morale, so I can only advise that paediatricians should read it too, and make it compulsory reading for nurses, physiotherapists, teachers, and others who may deal with haemophilic children.

D I K EVANS
Consultant haematologist

Manual of Infections and Immunizations in Children. Edited by Peter Rudd and Angus Nicoll. (Pp 291; £12 paperback.) Oxford Medical Publications, 1991. ISBN 0-19-262118-1.

Inoculation against smallpox appears to have been first used in the 6th century BC by the Chinese, who implanted bamboo splinters dipped in pustular material into the nasal mucosa of uninfected individuals. The protective effect of cowpox against natural smallpox infection was folk wisdom for many generations before Jenner. Over the last hundred years immunisation has been an even larger contributor to the health of individuals and nations. With the development of gene manipulation by molecular biology, and the ability to produce purified antibody by *in vitro* techniques, its day is only just dawning.

This book then appears at a watershed in the development of immunisation, and provides a bridge linking scientific and academic knowledge on the one hand, with everyday clinical practice on the other. It has been rapidly and professionally put together by the British Paediatric Association Standing Committee on Immunisation and Vaccination.

The book is directed towards all concerned in paediatric primary care, junior hospital staff, paramedical staff, and parents, and is divided into sections. The first of these discusses the general diagnosis and management of common infections in childhood from a problem orientated viewpoint, for example, the child with a rash and the child with vomiting and diarrhoea. The second section provides short summaries of specific childhood infections, with particular detail of recently recognised conditions such as AIDS and Kawasaki disease.

This is followed by a short section on the collection of specimens for laboratory diagnosis and a long and comprehensive section on immunisation, including a very helpful discussion on practical problems: should you immunise a child with diarrhoea or a chest cough when they come to clinic? What about the baby who is said to have had whooping cough or measles? What is the relevance of a history of fits or febrile convulsions?

The book concludes with detailed advice on travelling abroad with a child, a series of

useful appendices, and a bibliography for further reading.

This second edition has been expanded and brought up to date and is beautifully laid out, simple, straightforward, and authoritative. Demanding a place in every GP's surgery, accident and emergency unit, and in every general paediatric ward in the country, it is a model of clarity and accuracy. I only wish all medical texts were half as good as this.

MICHAEL TARLOW
Senior lecturer in paediatrics

Paediatric Speciality Practice for the 1990s. Edited by Janet Byre and Robert Boyd. (Pp 275; £20 softback.) Royal College of Physicians, 1991. ISBN 1-873240-19-8. Available from the Royal College of Physicians of London, 11 St Andrews Place, Regent's Park, London NW1 4LE.

My personal paediatric library is kept up to date by the editors of the *Archives* supplying me with excellent books, ostensibly for review. I'm beginning to wonder though, is this just kindness or a subtle hint? Have the editors heard something that I haven't?

This latest splendid edition to my bookshelf is based on the most recent paediatric conference held at the Royal College of Physicians. A number of distinguished subspecialists review changes in practice over the last five years, and speculate on how these will influence paediatrics in the next decade.

The book begins with community paediatrics, stressing prevention of illness and promotion of good health. The importance of information systems, review of surveillance, and integration of services are discussed. Full implementation of best current practice is seen as the goal over the next few years.

Most subspecialties (neonatology is deliberately excluded) are represented with the sad exceptions of accident and emergency, the largest, and intensive care, the most expensive. The chapters include up to date opinion on aetiology, investigations, and treatment. For example there is a thought provoking review on the aetiology on cerebral palsy, and in addition the author stresses the present and probable future role of surgery and highlights the tremendous importance of counselling performed by physiotherapists, largely untrained for psychotherapeutic work. The chapter on epilepsy illustrates the circle fully turned with the use of magnetic resonance imaging to detect small focal lesions in the temporal lobe with subsequent surgical removal. A useful resumé of risk versus benefit of drug treatment follows.

Opinions are revised on what were sometimes overkill investigations. Thus under 'imaging of the urinary tract', cystography is not even mentioned, and the ESPGAN criteria of three jejunal biopsies for the diagnosis of coeliac disease is being abandoned.

The philosophy of changes in treatment is epitomised by the chapter on paediatric oncology headed 'towards cure at least cost'. For many malignancies current research is aimed at identifying poor prognostic groups for more intensive treatment while reducing treatment for cases with a good outlook.

Current new treatments, such as pancreatic transplant, and somatic gene therapy are discussed with their attendant difficulties, which surely will be overcome in the next 10 years. The book concludes with a thoughtful

chapter on the role of general practice in child care.

I have mentioned just a few of the enormous number of ideas in this book. It is well presented and contains references up to 1990. As today's subspeciality work becomes part of tomorrow's general paediatrics all those involved in child care will find it very useful. The editors and authors are to be congratulated and so is the Royal College of Physicians.

M MONCRIEFF
Consultant paediatrician

Pediatric Decision Making. 2nd Ed. by Stephen Berman. (Pp 480; £39.50 hardback.) B C Decker Inc, 1991. ISBN 1-55664-141-9.

Although not the sort of book that you can leaf through idly in free moments between bathing the baby and writing your MD, it is a very comprehensive approach to paediatric management. Written as a series of flow diagrams, it gives clear and sensible guidelines on common paediatric problems. It is divided into 14 sections according to systems and includes a section on behavioural and developmental disorders. Each section is further subdivided into chapters based either on presenting symptoms or on a presumed diagnosis. Important points to be covered in the history and examination are outlined, investigations are suggested according to the severity of the illness, and flow diagrams guide the reader through a logical sequence of management decisions, including follow up. All suggested drugs are listed at the ends of chapters together with dosages and availability. For simplification, diagrams are annotated separately on facing pages.

As it is an American book there are, of course, differences in names of drugs and recommended treatments. For example, subcutaneous adrenaline is still a commonly used first line bronchodilator in America where it is prescribed as subcutaneous epinephrine. In addition there are differences in our antibiotic prescribing policies and anyone using this book should be aware of their local policy, particularly when prescribing first line antibiotics for undiagnosed septicaemia or meningitis.

Every registrar should keep this useful book on hand for reference should they wish to appear intelligent to their senior house officers, especially from the end of the phone in the middle of the night. However, it is not pocket sized, and at nearly £40 it is probably a book

to keep under lock and key on the children's ward.

SUSAN LAURENT
Senior registrar

Child Health Matters. Edited by Sally Wyke and Jenny Hewison. (Pp 156; paperback.) Open University Press, 1991. ISBN 0-335-09393-0.

When I went for one of my first interviews for a paediatric job I was asked by one of the interviewers whether it would make any difference to my clinical practice if I were a parent. At the time I said it would (thinking that must be the right thing to say), now I am convinced. It has changed my practice because I have had to look at child health from a different perspective. In many ways this book succeeds in doing the same thing in that it enlightens the reader about a parent's eye view of services and child health in general.

It is a modern, politically up to date book that provides a mixture of social, psychological, medical, and environmental emphases. The contributors come from a wide variety of backgrounds and there is a useful summary of each chapter in the book at the beginning that acts as a useful way of orientating the reader.

Jenny Popay's chapter on 'women, child care and money' raises many issues including health professionals' need to stress the importance of what women living in poverty can do and *not* what they cannot, the concept of relative poverty related to lack of control of financial assets within a family, the role of the extended family in supporting mothers on low income, the need for jobs, access to money and good quality child care, and the need for health care provision for mothers themselves. The same chapter emphasises how a mother's and health professional's concepts of normality often differ and the methodological difficulties of getting mothers to talk about 'minor' problems. There is a constant need to be *seen* to be dealing appropriately and mothers feel very anxious about health professionals' attitudes to them. The importance of reassurance in general is stressed again later in the book in Clark and Hewison's chapter on 'whether or not to consult a GP', and half the sample of parents who were questioned stated that reassurance was the single most important thing that they received from their doctors. This certainly re-enforces my own belief that reassurance must be built in as a valid outcome measure for health services offered to children.

'Social and cultural assumptions have serious consequences when they serve as measures of "normality" in the area of child development'. In the chapter on 'understanding the needs of ethnic minorities' this idea is well explored using the concept of the childhood/adulthood continuum and the differential emphasis placed on the tools (toys) in contrast to the context of play to illustrate different perspectives. We are told about how certain health education exercises have shown an insensitivity to parents needs and knowledge, including the Surma story and misguided health advice given to women wishing to fast during Ramadan. It is obvious there are many conflicting religious, family, and health demands made on women in these groups.

Throughout the book one gets the impression that sociological research methodology may be less rigorous in its nature, but one certainly gets more of the 'feely' stuff that is so important for the new NHS, and yet does not appear to have been so readily accepted by the scientific community as yet. Contrasts between health professionals and parents are brought out in the other chapters on ideologies of child care and an interesting chapter on the use of services by parents of children with cough. This certainly dispels the myth of unnecessary service usage by using the interesting technique of scenario presentation and producing a severity threshold. Later chapters provide extremely useful reviews on breast feeding and asthma. The latter places emphasis on nurse run clinics, the need for adequate time to educate children and adults in the treatment techniques required, and the usefulness of district based asthma working groups. Jenny Kitssinger's chapter on 'child sexual abuse and the trials of motherhood' re-enforces the often neglected perspective of the mother and her own needs after the disclosure. Jacqueline Mok's chapter on 'HIV' gives up to date practical guidelines for monitoring and treatment of HIV infection in children and the concept of the 'family clinic' set up in Edinburgh, which provides a well functioning community, social services, education, and health interface.

Overall, this is an excellent pot-pourri of material that borrows data from many disciplines involved in child health, including sociology, psychology, medicine, and social anthropology. Child health cannot be seen as the province of one discipline only and this book certainly demonstrates how different disciplines can work together to give a fuller picture and, hopefully, influence a group of more empathic doctors.

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Dexamethasone and meningitis—more evidence

For the story so far see Archivist 1991;66:137. Now a study done in Costa Rica has been reported by a team including Dr McCracken (Carla M Odio and colleagues, *New England Journal of Medicine* 1991;324:1525–31).

They studied 101 children with bacterial meningitis admitted to the National Children's Hospital in San José of whom 90% were less than 5 years old. Because antibiotic treatment causes a massive release of endotoxin into the cerebrospinal fluid with a consequent surge in the mediators of inflammation (cytokines) the dexamethasone in this trial was given 15 to 20 minutes *before* the first dose of antibiotic (all the patients were treated with cefotaxime). Random assignment resulted in 52 patients receiving dexamethasone and 49 placebo. Eighty two per cent of the placebo group and 75% of the dexamethasone group had *Haemophilus influenzae* meningitis. Lumbar cerebrospinal fluid pressures were measured initially and after either 12 or 24 hours.

The dexamethasone treated children had a significantly quicker rise in glucose in the cerebrospinal fluid and falls in cerebrospinal fluid white cells, protein, tumour necrosis factor α , and platelet activating factor. They also had a significantly greater fall in cerebrospinal fluid pressure and rise in cerebral perfusion pressure at 12 hours.

The clinical condition as assessed by the Glasgow coma scale and the Herson-Todd prognostic score was significantly better at 24 hours in the dexamethasone treated children and prolonged fever was much more common in the placebo group. One child in each group died. Neurological sequelae occurred in 31% of the placebo group and 10% of those given dexamethasone ($p=0.008$). In contrast with previous studies the decrease in hearing loss in the dexamethasone group was not statistically significant (6% *v* 16%, $p=0.18$). Neurological sequelae or hearing loss occurred in 14% in the dexamethasone group and 38% in the placebo group ($p=0.007$, relative risk 3.8, 95% confidence interval 1.3 to 11.5). Ultrasound or computed tomography showed cerebral atrophy, ventricular dilatation, or cerebral infarction in 14% and 29% ($p=0.06$).

I'm convinced. There seems now to be very little room for doubt that dexamethasone is beneficial, at least in *H influenzae* meningitis and there is, as far as I know, no reason to believe that meningitis due to other bacteria reacts differently.

The same issue of the *New England Journal of Medicine* contains an extremely thought provoking debate about the ethics of clinical trials.^{1 2} Modern therapeutics is, of course, to a large extent based on the results of randomised clinical trials and nobody doubts their scientific value. Trials of dexamethasone in meningitis were justified because whether it would prove beneficial or not was truly an open question. Now, I would hesitate to introduce further patients into a dexamethasone/placebo trial. The difficulty arises particularly with severe or fatal illnesses where the patient does not get a second chance if assigned to the wrong group. Patients are entitled to expect that their doctors will offer them the best possible available treatment according to their knowledge *and belief*. Can a doctor ethically offer a treatment which he believes (but does not know) is likely (but not certain) to be inferior? Increasing patient knowledge and demands for truly informed consent are bound to force the issue. Patients, for instance, are unlikely to feel obliged to accept the conventional demand for a 5% level of statistical significance. I think we are in for a very vigorous debate.

ARCHIVIST

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2 Passamani E. Clinical trials—are they ethical? *N Engl J Med* 1991;324:1589–91.

ARCHIVES OF DISEASE IN CHILDHOOD

The Journal of the British Paediatric Association

Annotations

Smoking in children

Prevalence and time trends in adolescent smoking

The prevalence of smoking has been declining in all adult age groups in Britain since the 1960s, with this decline accelerating in the 1970s. Prevalence rates fell from 52% of men and 41% of women in 1972, to 33% and 30% in 1988.¹ This decline has been more noticeable in men, resulting in a narrowing of the gap between male and female smoking prevalence. Although this trend has been seen in all adult age groups, it has been more striking in younger smokers, and, as shown by data on the under 16s, has resulted in a reversal in the traditional position where males smoked more than females. Although men generally consume a larger number of cigarettes, the trend is toward female smokers increasing the number of the cigarettes they smoke.¹ There has been an increasing trend toward the promotion of low tar cigarette brands on the market, and it has been suggested that the manufacturers may particularly target women as potential consumers for this product. This is borne out by the greater proportion of women smoking 'low tar' (less than 10 mg/cigarette) brands (25%) than men (16%).¹

A large proportion of adult smokers acquire their habit during childhood or adolescence. The trends, therefore, in the smoking habits of young people are of major importance for health educators. Amos estimated that there are over 500 000 smokers aged 11–15 years in Britain, with about 100 000 of them likely to die as a result of their tobacco consumption.² Goddard and Ikin have described declining smoking prevalence in 15–16 year old boys and, worryingly, a stable or slightly increasing prevalence in girls of the same age, such that in 1988, 24% of boys and 31% of girls were smoking either regularly or occasionally.^{3,4} Although at much lower prevalence, this gender reversal was also true for 14–15 year olds from 1984 to 1988 (15% of boys and 19% of girls in 1988), and to a lesser extent in even younger children. It seems that health education on smoking, although having met with some success in boys, seems to have failed to address the problem in girls.

It seems that this is not only a British phenomenon. Swan *et al*⁵ documented similar reversals for the US in 12–17 year olds in the late 1970s,⁶ in Canada in 15–19 year olds in the early 1980s,⁷ and in New Zealand,⁸ Australia,⁹ Norway,¹⁰ and Sweden.¹¹

Factors associated with the uptake of smoking in children

The literature on the factors associated with the uptake of smoking is vast. Flay *et al* described the mechanism by which smoking behaviour is established.¹² It seems there is

a transition in behaviour through a preparatory stage during which attitudes are formed, an initiation phase which involves trying it out, an experimentation phase during which children learn how to smoke, and finally the transition to being a regular smoker. It seems likely that most children will experiment with smoking, but it is the transition from this to regular or 'adult' smoking that is crucial and on which health education must focus.

Although studies since the early 1980s have produced valuable cross sectional data on smoking prevalence,^{3,4} longitudinal studies are also required to study this phenomenon further. Swan *et al* describe a longitudinal study of adolescent smoking which enabled the authors to observe changes in behaviour and attitudes in a cohort of children followed from age 11–12 years to age 21–22 years.¹³ This study reiterates the distinction drawn by Flay between 'experimental' and 'regular' smoking. Although it appeared from this study that the greatest incidence of regular smoking was around the age of 14 years, experimentation occurs much earlier and results in a softening of attitudes towards smoking (for example with children becoming dismissive of the hazards associated with smoking). This has important implications for health education as, if experimentation cannot be prevented, health educators must be aware of the need to reinforce negative attitudes towards smoking at this vulnerable time before regular smoking is established. Swan *et al* took the view that if regular smoking could be deterred beyond ages 15–16 years, then it was much less likely to occur at all.¹³

Goddard also conducted a longitudinal study of children in their second, third, and fourth year of secondary education.¹⁴ She identified a number of risk factors associated with children starting to smoke. These included siblings smoking, parents smoking (but only having an independent effect if siblings do not smoke), poor educational aspirations, and coming from a lone parent family. In addition, views about smoking were found to be important precursors of smoking behaviour but Goddard did not believe that the relationship between attitudes and behaviour was as rational in children as it is in adults. Most interestingly, however, was Goddard's finding that simply 'being a girl' was an independent risk factor for starting to smoke: that is, the greater propensity of girls to smoke was not attributable to any other risk factor identified in the analysis. Each of the risk factors identified in the analysis had small effects but of similar magnitude, indicating the complex and multifactorial nature of this problem.

The most frequently documented factors associated with uptake of smoking can be divided, therefore, into four

categories: (i) attitudes and beliefs (for example awareness of the health hazards, self image); (ii) characteristics of the family, school, and social environment (for example parental and sibling attitudes and behaviour, school attitudes, involvement with friends of the opposite sex); (iii) advertising and the external environment (including acceptability of smoking, availability of cigarettes); and finally (iv) the characteristics of health education interventions (for example teacher led, peer led, parental involvement).¹⁵ Health education must be designed to tackle each of these areas.

Health education interventions

In the past there has been only limited success achieved by interventions aimed at reducing the prevalence of adolescent smoking. Early interventions depended on 'fear arousal', a technique not now thought to be particularly useful. Subsequent interventions have focused on either changing knowledge and attitudes (based on the premise that changes in behaviour will follow) or those which focus on the development of social skills to resist pressures to smoke.

Interventions that have merely used information to try and dissuade children from smoking have not met with a great deal of success.^{16 17} Those that have coupled this information with attempts to change attitudes have been rather more successful, particularly if parents have been involved with the programme.¹⁸ Interventions that have attempted to equip the child with the skills necessary to resist smoking have also generally achieved some success, at least in the short term.¹⁹ However, many of the studies documented suffer from methodological weaknesses, frequently with biased or small samples. The long term effect of many interventions remains unknown. Good longitudinal surveillance remains an essential prerequisite for properly targeted health education.

The task for health education

Despite the greatest incidence in children's smoking occurring around the age of 14 years it seems likely that, in order to deter the experimental smoker from becoming the regular smoker, interventions to reinforce negative views of smoking need to occur much earlier than this, around the time of likely experimentation.

As the smoking habits of parents, siblings, and teachers are important precursors to adolescent smoking, it is important that the health education of young people is not balkanised, and is seen as part of a broader health promotion strategy, based on the notion of health as a positive attribute, rather than always focusing on ill health and victim blaming. An effective policy to reduce adolescent smoking must promote non-smoking as the norm in the home, at school, and outside in the external environment.

Considerable variation seems to exist in the prevalence of smoking in children, and there must be reliable baseline estimates made before curricula are developed, in order that the effectiveness of health promotion activities can be assessed. Provision of information on health effects, although important, will not alone be successful. It is vital that the other important issues identified in the literature are explored and skills are taught that will help young people to resist the pressures on them to start to smoke.

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Acute appendicitis in the preschool child

Acute inflammation of the vermiform appendix is probably as old as man. An Egyptian mummy of the Byzantine era exhibits adhesions in the right lower quadrant, suggestive of old appendicitis.¹ That it may become inflamed was recognised by case reports of postmortem examinations in the 1700s and the term perityphlitis was used. Fitz was first to use the term appendicitis and recognised that removal of the inflamed appendix could result in the cure of what had previously been an almost universally fatal condition.¹

The three major advances in the management of acute

appendicitis have been: improved fluid resuscitation, better anaesthetic techniques, and the introduction of antibiotics—more importantly those with activity against anaerobes. Despite these major advances, however, acute appendicitis remains the cause of substantial morbidity.

Overview

Acute appendicitis in the preschool child is rare and accounts for less than 5% of all paediatric admissions with

that diagnosis.² It appears to be slightly more common in boys than girls. It therefore presents a diagnostic challenge for both the general practitioner and the admitting surgeon. Between 26–36% of patients with perforated appendicitis had sought advice from a healthcare professional before admission and surgical intervention had not been initiated.^{3–4} The fundamental premise is that earlier diagnosis of acute appendicitis leads to a better clinical outcome. The greater the delay, the greater the risk of perforation.^{4–6} Perforation is associated with a greater morbidity. This is manifest as postoperative septic complications and a longer hospital stay with its associated psychological morbidity.⁶

The perforation rate, however, remains high in the preschool child, approaching 90% in one series.⁴ Some workers have suggested that this is due to a thin walled appendix in the child predisposing to early perforation. Indeed in experimental studies Tsuji *et al* have demonstrated gangrenous changes as early as eight hours after appendiceal luminal obstruction.⁷ Others attribute the higher perforation rate to a delay in diagnosis.^{2–4} The reason for this delay is probably multifactorial. The ill child finds it difficult to localise pathology accurately and then communicate to the parents. Parental delay has been identified as a factor contributing to delayed diagnosis.⁸

Presentation and diagnosis

The mainstay of diagnosis remains a detailed history and careful physical examination. The child may have non-specific symptoms, for example, irritability, restlessness, crying, etc. Associated illness, for example, upper respiratory tract infection, otitis media, and gastroenteritis are often present and this may further confuse the clinical picture.^{9–10} This may help to explain why 11–24% of these children are admitted to an inappropriate medical service (N Williams, L Kapila, unpublished data).² Vomiting is the most frequent symptom in this age group and is present in 75–81% of children.^{2–4} Abdominal pain is not invariably a feature of acute appendicitis but is the next most common symptom. It is more likely to be central than confined to the right iliac fossa. Shift of pain is also less likely in the preschool child. Aggravation of pain by movement and coughing is good evidence of peritoneal irritation. Anorexia, poor feeding, and loss of appetite are also good indicators of an intra-abdominal inflammatory process. Sleep disturbance may be present in over half of cases.¹⁰

Examination of the very young child in this situation needs patience above all else, otherwise valuable physical signs will be missed in a nervous, anxious child who has just been hospitalised. Tachypnoea may be noticed and can easily be mistaken to indicate a chest infection. It should be remembered that young children inspire with their diaphragms and in the presence of peritonitis they take shorter quicker breaths because of pain inhibition. The physical examination may be rendered more fruitful and informative if carried out in the mother's lap. Initial observation will permit an overall clinical impression and allow time for detection of more subtle physical signs, for example, abdominal wall movement with respiration. Fever is present in up to 90% of cases of appendicitis. However a normal temperature does not exclude a perforated appendix.¹¹ The pulse rate on admission is very likely to be affected by anxiety and so isolated readings are of little value. The importance of a sustained tachycardia as a sign of peritonitis is clear, frequently in excess of 120 beats/minute.¹⁰ Local tenderness is present in up to 95% of children with non-perforated appendicitis but in less than 55% of those with perforated appendicitis.⁴ Diffuse tenderness but with maximal intensity in the right iliac fossa is indicative of more advanced disease. Guarding is a more

objective sign than tenderness but is not as easy to elicit because it is vital to have the child comfortable and relaxed. This may be difficult in an ill, apprehensive child. In this situation light sedation with diazepam or trimeprazine then re-examination may prove beneficial. Not only will the child be more settled, but it will give the surgeon time to assimilate the history and to observe the child at a distance for a while. Auscultation of the abdomen may be useful as absent bowel sounds increases the likelihood of intra-abdominal pathology. The preschool child is more likely to have an appendix mass at presentation. This may create a management dilemma. Conventional thinking is to treat those masses that are palpable preoperatively with intravenous fluids and antibiotics. However up to 55% of masses are only palpable under anaesthetic.¹² Some advocate continued conservative management and would not proceed to appendicectomy if a mass was palpable under general anaesthesia.^{2–12} However other data suggests that early appendicectomy produces comparable if not superior results and the hospital stay is greatly reduced.^{6–13}

The value of rectal examination can only be determined by the assessing surgeon in individual cases. Clearly if a decision is made to operate then it has no part to play. However in doubtful cases and in cases of pelvic appendicitis when the abdominal signs are equivocal rectal examination may prove useful. The elicitation of rebound tenderness has no part to play here; it is cruel and provides no additional information that cannot be otherwise inferred.

Of all paediatric surgical admissions with abdominal pain only approximately 35% will need surgical intervention.^{9–10} Not all of those are obvious at initial assessment and so other ancillary methods and investigations must be employed to further distinguish those who have a surgical cause for their abdominal pain and those who do not. First and foremost there is no substitute for repeated reassessment and re-examination of the child by the same surgeon. Jones calls this 'active observation' if only to confirm its implementation as an active management decision and to focus attention on repeated reassessment.¹⁴

Investigations

The value of haematological investigations is dubious and needs to be seen in perspective.¹⁵ The only value of the white cell count would seem to be to prompt observation rather than operate in a patient who has equivocal features of appendicitis together with a normal white cell count. Plain abdominal radiography for diagnosing acute appendicitis is based on the presence of one or more of the following signs: faecolith of the appendix, gas in the appendix, air-fluid levels, or dilation of the local bowel (that is, sign of paralytic ileus). However not one of these signs is specific for acute appendicitis and may be found in patients with other causes of pain in the right iliac fossa. Ultrasound assessment lends itself particularly well to this age group because of its non-invasive nature. If the appendix can be seen on ultrasound examination this is taken to indicate the presence of acute appendicitis. If the organ cannot be seen appendicitis is excluded. Rubin and Martin reported a sensitivity of 89% and a specificity of 92% in a cohort of 110 children. In this group three were clinical false positives, however all three had negative ultrasound scans.¹⁶ They also managed to exclude 11 patients in whom the cause of abdominal pain was gynaecological. Clearly ultrasound has a part to play in the diagnosis and management of abdominal pain in childhood and the early reports in the literature has demonstrated its value. Its role in detecting an appendix mass/abscess should obviate the need for an examination under anaesthetic.

Barium enema examination has been reported in adults

with variable success. It may be non-diagnostic or unsatisfactory in up to 16% of cases.¹⁷ Its use in children is likely to be restricted by its uncomfortable nature and the fact that the patient is receiving a dose of radiation.

Conclusion

Clearly the way ahead in reducing the morbidity from acute appendicitis in the preschool child is in early diagnosis. This theoretically will reduce the perforation rate and so reduce the septic complication rate and the hospital stay. It is important to appreciate that delays occur both in the community and once the child is in hospital. A greater awareness among healthcare professionals and among parents who may then seek medical advice sooner appear to be the initial steps. However once the child is in hospital every effort should be made to ensure prompt and accurate diagnosis and then the institution of appropriate treatment. The childhood mortality rate in the UK is presently less than 0.00 per 1000 live births. The decade 1976–85 witnessed 105 childhood deaths from acute appendicitis, of whom 29 were under 5 years of age and five were neonates.¹⁸ Thus although the preschool child accounts for less than 5% of admission in this cohort, they comprise >30% of the mortality. The last century has witnessed the decline in mortality from acute appendicitis from invariable to very rare indeed. Perhaps the next few decades will see a corresponding fall in the morbidity in this especially high risk group, the preschool child.

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Screening for neuroblastoma

Neuroblastoma is the most common extracranial solid tumour of childhood with an incidence of 6–10 cases per million children (under 15 years) each year.¹ The median age at diagnosis is 2 years and few children are diagnosed after 5 years of age. The tumour originates in the adrenal gland in half of the cases and elsewhere in the abdomen in a further 20%. The remaining tumours arise in sympathetic ganglia in the thorax, pelvis, or neck. Children presenting with localised, resectable (stage 1) tumours can be treated by surgical excision with a high expectation of cure (95% five year survival).² Unfortunately, symptoms from the disease are non-specific (anorexia, malaise, limb pain, etc) such that over 50% of clinically presenting children will already have advanced metastatic (stage 3 or 4) disease.² For these children prognosis is very poor (25% five year survival)³ despite such intensive and expensive treatment as delayed primary surgery, chemotherapy, radiotherapy, and high dose chemotherapy with bone marrow rescue. In addition, neuroblastoma has not shown the dramatic improvement in prognosis over the past 10–15 years seen with other childhood malignancies such as acute lymphoblastic leukaemia, Hodgkin's disease, and Wilms' tumour.⁴

The aim of screening is to detect disease preclinically so that children can be treated when younger and with lower stage disease. As children diagnosed under 1 year of age with localised neuroblastoma are known to have a much better prognosis than older cases,⁵ screening for neuroblastoma is attractive and might be expected to reduce the morbidity and mortality. How, then, can we screen for neuroblastoma?

Children with neuroblastomas have long been known to excrete catecholamine metabolites in their urine.⁶ When La

Brosse presented a simple test for 4-hydroxy-3-methoxy-mandelic acid (VMA) using urine spotted onto filter paper mass screening for neuroblastoma became a possibility.⁷ Sawada *et al* were the first to begin mass screening in 1972, testing 42 636 children aged 3 years in Kyoto, Japan, and finding one child with stage 2 disease.⁸ Mass screening has advanced rapidly in Japan since that time: Nagoya joined the programme in 1977 and Osaka in 1980 and by 1985 a nationwide programme for mass screening was introduced. The age at which children are screened has been reduced to 6 months and the qualitative VMA spot test has been superseded by quantitative measurement of both VMA and homovanillic acid (HVA) by high performance liquid chromatography (HPLC). All 3 month old infants are examined under the Child Health Survey Programme and at this time parents are given a screening kit. When the infant is aged 6 months a urine sample is taken and the filter paper is mailed to the local screening centre. Children with values above mean +2.5 SD for VMA and/or HVA are examined physically, by chest and abdominal radiography, and by abdominal ultrasound scan. By the end of 1988, a total of 4 018 630 children had been screened (78.9% of all infants) and 342 cases of neuroblastoma had been found, an incidence of 1/11 750.

Dr Sawada and his colleagues have presented extensive data regarding the outcome of children detected by the screening programme.^{9–11} Seventy eight percent of cases were detected between 7 and 9 months of age, and 95.8% of children were asymptomatic. By the end of August 1989, fully 97% of these children were still alive and only three children had died from progressive disease. There has also been a shift away from advanced stage disease at diagnosis

(55% had stage 4 disease during 1971–6 compared with 8% in 1989) towards children presenting with localised disease (20% stage 1 and 2 1971–6 compared with 65% in 1989). Is there, then, any doubt about the value of screening?

Unfortunately, there have been no population based control trials to study the impact of mass screening for neuroblastoma.¹² Results from any screening programme must take into account lead time bias and length bias. Lead time bias refers to the apparent increase in survival of a case being detected earlier in the course of the disease as a result of screening. Length bias is due to slower growing tumours having a longer preclinical phase of the disease and thus a greater chance of being detected by screening than faster growing, more aggressive tumours. Where screening has been introduced without adequate control studies it is, therefore, possible that improvement in survival may be due in part to the bias of screening.¹³ Also there are features of neuroblastoma that makes interpretation of the results from Japan difficult.

Neuroblastoma is known occasionally to regress spontaneously without treatment,¹⁴ and there is evidence that some of the tumours detected by screening might never have come to clinical attention had they not been detected by the urine test. First, the incidence of clinically detected tumours in a screened population ranges from 1/17 000 to 1/10 000.¹⁵ When screening by HPLC was introduced in Japan, the incidence was seen to increase to around 1/8000–1/5000 suggesting that some 'silent' neuroblastomas were being detected.

Secondly, comparison of prognostic markers between cases detected clinically and by screening suggests that screening picks up tumours with an inherently better prognosis. MYCN oncogene copy number, chromosome 1p loss of heterogeneity (1pLOH), and DNA ploidy have been shown to have strong prognostic significance.^{16–18} Cases detected by screening tend to have single copy MYCN, no 1p LOH, and aneuploid tumours.¹⁹ On the other hand clinically detected tumours, particularly those negative at an earlier urine test, tend to have tumours with amplified MYCN, 1p LOH, and diploidy. As the above markers are consistent throughout the course of the disease,²⁰ screening as currently undertaken may be failing to detect the very cases being sought, that is, those with a poor prognosis.

In addition, for urine analysis to be positive, the tumour must have reached a critical size. Few tumours have been detected under 3 g with the majority weighing between 10 and 50 g at diagnosis.⁸ Some tumours may be missed when the child is screened at 6 months of age because the tumour was too small at that time to produce raised concentrations of metabolites.

Finally, epidemiological studies have shown that 18% of cases of neuroblastoma present before the age of 6 months.²¹ Indeed, with increasing use of antenatal ultrasound scanning, neuroblastoma can be detected before birth.²² Screening at 6 months obviously will not affect the clinical outcome of such cases.

In order to assess the value of screening, centres in Quebec and the United States are cooperating in a controlled trial whereby neuroblastoma cases seen in the province of Quebec (where over 90% of 3 week old neonates and over 70% of 6 month old children are being screened) will be compared with cases seen in Quebec before screening, and with cases seen in Ontario, Minnesota, Florida, and the Greater Delaware Valley where there is no screening policy.²³ Craft has also proposed a controlled trial involving six regions in the UK (A W Craft, personal communication). It is likely to be five to eight years before the results from these trials are available, but it is important that such controlled studies are implemented before widespread arbitrary urine testing renders such research impossible.

If the above studies show that screening for neuroblastoma can reduce the morbidity and mortality from the disease, and cost-benefit analyses are favourable, what methods are available for screening? Urine may be collected from a napkin onto a filter paper, which is then dried and mailed to the screening centre. To increase compliance the help of health visitors may be enlisted, but then the timing of collection should coincide with a routine visit in order to reduce costs. Most screening is now performed at 6 months of age, but this may not be the ideal time and screening later, for example at 18 months, may detect better the more aggressive tumours. Multiple testing may also be desirable. Once in the laboratory, VMA and HVA may be measured by thin layer chromatography (TLC),²⁴ HPLC,²⁵ gas chromatography with mass spectrometry (GC/MS),²⁶ or by enzyme immunoassay.²⁷ The method chosen should combine low cost with high sensitivity and specificity. Normal values should be determined within each laboratory, cut off concentrations being set to reduce the possibility of false negative results while minimising the parental anxiety of false positive results. The majority of laboratories employ mean $\pm 2-3$ SD. Once detected, the infant should receive rapid, sympathetic, and up to date diagnostic confirmation and treatment.

Sawada and his colleagues in Japan are to be congratulated on their extensive pioneering work on neuroblastoma screening. Much has been learnt about this enigmatic tumour. Screening is not yet of proved value and the results from Japan and Quebec are eagerly awaited. In the mean time, it is important that every opportunity be taken to study this tumour and anyone involved in establishing a screening programme should at the same time gather controlled epidemiological data and clinical and biological details from cases detected both clinically and by screening.

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- † Iron supplementation should therefore be considered from around 6 weeks.



ORIGINAL ARTICLES

Height reduction in 539 tall girls treated with three different dosages of ethinyloestradiol

E K Normann, O Trygstad, S Larsen, K Dahl-Jørgensen

Abstract

During the period 1970 to 1985, 539 constitutionally tall girls were treated with ethinyloestradiol in varying dosages to reduce final height. They all had a predicted final height above 181 cm ($>+2.5$ SD). The girls were all healthy and were treated with three different dosages of ethinyloestradiol. Throughout these 15 years recommended treatment regimens changed, and the treatments described followed these guidelines. Girls in group 1 ($n=263$) were treated with 0.5 mg of ethinyloestradiol, group 2 ($n=178$) with 0.25 mg, and group 3 ($n=98$) with 0.1 mg. The total mean (SEM) reduction of final height was 5.9 (0.2), 5.3 (0.1), and 4.4 (0.2) cm when treated with 0.5, 0.25, and 0.1 mg respectively. Group 1 was treated for 2.02 (0.03) years and group 2 and 3 for 1.85 (0.04) and 1.63 (0.05) years respectively. When expressed in relation to the treatment period the reduction of final height was 3.0 (0.1), 3.1 (0.1), and 2.9 (0.2) cm/year of treatment respectively. All the girls were treated with ethinyloestradiol as a daily single dose, while progestogen was given daily the first 10 days of every month.

In conclusion we found that a daily dose of ethinyloestradiol 0.1 mg for about 20 months is sufficient to reduce final height. We recommend starting treatment at a bone age of about 12 years.

Tall stature is usually defined as body height of $>+2$ SD above the population mean.¹ In Norway the average final height is 167.3 cm in girls. According to this definition, tall stature in Norway is final height above 178.3 (SD 5.5) cm.² In 1956 Goldzieher introduced oestrogen as treatment of excessive growth in adolescent girls.³ Since then there have been several different regimens for treating tall girls. Many investigators used conjugated oestrogens, and others used ethinyloestradiol, in varying dosages, usually combined with a progestogen 7-10 days each month to give regular vaginal bleeds. In the 1960s most practitioners used 0.5 mg of ethinyloestradiol, 0.25-0.30 mg in the 1970s, and in the 1980s there have been reports indicating that 0.1 mg is sufficient.^{1 4-14} However, these studies include a relatively small number of patients ($n=5-100$).

Arterial thromboembolic complications and possible carcinogenic effects of the long term oestrogen treatment by contraceptive pills make it important to find the lowest dosage of oestrogen giving a satisfactory reduction of final height. We have compared the growth

reducing effect of three different dosages in 539 tall girls, demonstrating that low dose (0.1 mg) treatment is as effective as high dose (0.5 mg). Furthermore, we have studied the optimum age for start of treatment in relation to the treatment period needed.

Patients and methods

PATIENTS

During the period 1970 to 1985, 1143 girls were evaluated at the outpatient clinic of the Department of Paediatrics, The National Hospital (Oslo, Norway), because of tall stature. They all went through a full physical examination. Only girls with a predicted height above $>+2.5$ SD of the normal Norwegian population, corresponding 181 cm, were offered treatment. There were 539 of these girls; all accepted treatment and were enrolled in this study. The other girls were not followed up.

METHODS

Standing height was measured by a Holtain stadiometer and the bone age was estimated from a hand x ray film according to the Greulich-Pyle radiographic atlas.¹⁵ To reduce variation the bone age was determined by one of the authors only (OT) and one experienced paediatric radiologist. If their estimates differed by more than six months the x ray film was re-examined to reach agreement. The final height was predicted from the estimated bone age, according to the Bayley-Pinneau tables.¹⁶ The x ray film of 11 year old girls in the radiographic atlas of Greulich-Pyle caused problems because it is more mature than the picture of 12 year old girls. To get the correct bone age it was necessary to use the film of 13-13.5 year old boys instead (156 months of age) which corresponded to 11 year old girls (132 months of age).¹⁷ Concentrations of growth hormone, prolactin, oestrogen, progesterone, follicle stimulating hormone, and luteinising hormone and activities of aspartate aminotransferase and alanine aminotransferase were measured and found normal.

The 539 girls were all treated with ethinyloestradiol (Etifollin, Nycomed). In the late 1960s and the 1970s, 0.5 mg of ethinyloestradiol was used as a single dose combined with norethisterone 10 mg daily the first 10 days of every month (group 1, $n=263$). In 1981 ethinyloestradiol was reduced to 0.25 mg daily and norethisterone reduced to 5 mg the first 10 days of every month (group 2, $n=178$). In 1982 norethisterone was replaced with medroxypro-

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gesteroneacetate (MPA) 5 mg (Perlutex, Leo) because of the androgenic effect of norethisterone as hirsutism.¹³ In 1983 ethinyloestradiol was further reduced to 0.1 mg daily combined with 5 mg of MPA the first 10 days of every month (group 3, $n=98$). The girls in group 1 received a total dose of 396 mg, group 2, 169 mg, and group 3, 60 mg of ethinyloestradiol.

The girls were seen every fourth month at the outpatient clinic. They were measured, pubertal development stature was registered, and side effects noted. The bone age was estimated at six month intervals. Treatment was ended when the predicted final height was reduced to less than 180 cm, meaning that they would not become taller than about 180 cm after termination of treatment. They were followed up regularly until growth had stopped.

STATISTICAL METHODS

All results are expressed as mean values with either 95% confidence interval or SEM. The confidence intervals were calculated by using Student's procedure.¹⁸ All tests were carried out two tailed and the differences considered significant when the p values were less than or equal to 5%. The groups were compared by two way layout analysis of variance.¹⁹

Results

The auxological data at start of treatment showed no difference in chronological age, bone age, or height at start of treatment between the three groups (table 1). The predicted heights, final heights, and the reductions of final height in the three groups are shown in table 1. The difference between the groups in reduction of final height was significant ($p<0.001$). The duration of treatment was different in the three groups. When related to the different duration of treatment periods the height reduction was no longer significantly different between dosage regimens.

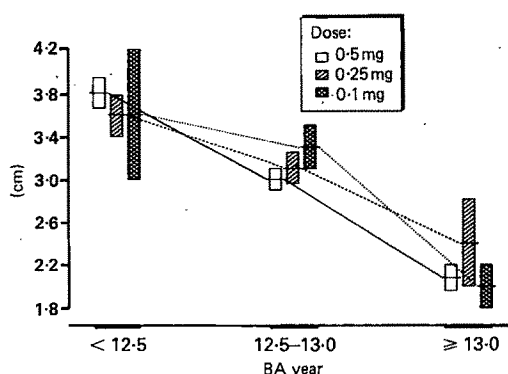
The groups were subdivided in relation to the bone age (table 2): <12.5 years, $12.5-13.0$, and ≥ 13.0 years. This gave us an opportunity to compare the effects of different dosages of ethinyloestradiol according to the bone age at onset of treatment. Because of the difference in treatment period between the groups it was necessary to compare the growth inhibiting effect after correction for the duration of treatment. For bone age <12.5 years the difference in reduction of final height between the three dosage regimens was significant ($p<0.001$). The difference between the groups in 'corrected' height reduction (cm/year of treatment) was not significant.

Table 1 Data from a study of 539 girls treated with three different dosages of ethinyloestradiol (95% confidence interval)

	Group 1 (0.5 mg)	Group 2 (0.25 mg)	Group 3 (0.1 mg)
No of patients	263	178	98
Chronological age (years)	13.2 (13.0 to 13.4)	13.1 (12.9 to 13.3)	13.8 (13.6 to 14.0)
Bone age (years)	12.6 (12.5 to 12.7)	12.6 (12.5 to 12.7)	12.7 (12.6 to 12.8)
Height at start of treatment (cm)	175.0 (174.4 to 175.6)	175.4 (174.8 to 176.0)	174.2 (173.6 to 174.8)
Predicted height (cm)	185.1 (184.7 to 185.5)	185.5 (185.1 to 185.9)	183.1 (182.7 to 183.5)
Final height (cm)	179.2 (178.8 to 179.6)	180.2 (179.8 to 180.6)	178.7 (178.3 to 179.1)
Reduction of final height (cm)	5.9 (5.5 to 6.3)	5.3 (5.1 to 5.5)	4.4 (4.0 to 4.8)
Treatment period (years)	2.02 (1.96 to 2.08)	1.85 (1.77 to 1.93)	1.63 (1.53 to 1.73)
'Corrected' reduction (cm/year of treatment)	3.0 (2.8 to 3.2)	3.1 (2.9 to 3.3)	2.9 (2.5 to 3.3)
'Relative' reduction (mm/mg ethinyloestradiol given)	0.16	0.31	0.73

Table 2 Data of 539 girls treated with ethinyloestradiol, divided according to bone age (95% confidence interval)

	Bone age (years)		
	<12.5	$12.5-13.0$	≥ 13.0
0.5 mg			
No of girls	104	72	87
Chronological age (years)	12.3 (12.1 to 12.5)	13.3 (13.1 to 13.5)	14.2 (14.0 to 14.4)
Height at start of treatment (cm)	171.8 (171.0 to 172.6)	175.5 (174.9 to 176.1)	178.3 (177.7 to 178.9)
Predicted height (cm)	185.8 (185.2 to 186.4)	185.5 (184.9 to 186.1)	183.9 (183.3 to 184.5)
Final height (cm)	178.2 (177.6 to 178.8)	179.5 (178.9 to 180.1)	180.2 (179.6 to 180.8)
Reduction of final height (cm)	7.6 (7.2 to 8.0)	6.0 (5.4 to 6.4)	3.7 (3.5 to 3.9)
Treatment period (years)	2.15 (2.03 to 2.27)	2.06 (1.96 to 2.16)	1.81 (1.74 to 1.89)
'Corrected' reduction (cm/year)	3.8 (3.6 to 4.0)	3.0 (2.8 to 3.2)	2.2 (2.0 to 2.4)
0.25 mg			
No of girls	47	91	40
Chronological age (years)	12.3 (12.1 to 12.5)	13.2 (13.0 to 13.4)	13.9 (13.7 to 14.1)
Height at start of treatment (cm)	172.4 (171.4 to 173.4)	175.6 (175.0 to 176.2)	178.7 (177.7 to 179.7)
Predicted height (cm)	186.1 (185.4 to 186.9)	185.5 (184.9 to 186.1)	184.8 (183.8 to 185.8)
Final height (cm)	179.5 (178.7 to 180.3)	180.2 (179.8 to 180.6)	181.3 (180.3 to 182.3)
Reduction of final height (cm)	6.6 (6.0 to 7.2)	5.3 (4.9 to 5.7)	3.7 (3.3 to 4.1)
Treatment period (years)	1.96 (1.80 to 2.12)	1.90 (1.78 to 2.02)	1.61 (1.45 to 1.77)
'Corrected' reduction (cm/year)	3.6 (3.2 to 4.0)	3.1 (2.9 to 3.3)	2.5 (2.1 to 2.9)
0.1 mg			
No of girls	14	52	32
Chronological age (years)	13.0 (12.4 to 13.6)	13.7 (13.5 to 13.9)	14.2 (13.8 to 14.6)
Height at start of treatment (cm)	170.7 (169.5 to 171.9)	173.9 (173.5 to 174.3)	176.2 (175.4 to 177.0)
Predicted height (cm)	183.3 (182.7 to 183.9)	183.3 (182.9 to 183.7)	182.5 (181.9 to 183.1)
Final height (cm)	178.1 (177.1 to 179.1)	178.3 (178.9 to 179.7)	179.4 (178.8 to 180.0)
Reduction of final height (cm)	5.2 (4.2 to 6.2)	4.9 (4.5 to 5.3)	3.1 (2.5 to 3.7)
Treatment period (years)	1.64 (1.38 to 1.90)	1.67 (1.55 to 1.79)	1.58 (1.36 to 1.80)
'Corrected' reduction (cm/year)	3.6 (2.4 to 4.8)	3.3 (2.9 to 3.7)	2.1 (1.7 to 2.5)



Reduction of final height (cm/year of treatment) in constitutionally tall girls treated with three different dosages of ethinyloestradiol, divided into groups depending on bone age (BA) in years. Bars indicate mean with 95% confidence interval.

In the group with bone age 12.5–13.0 years the height reduction was significantly different between the three dosage regimens ($p < 0.01$), but there was no significant difference between the groups in 'corrected' reduction.

In the most mature group (bone age ≥ 13.0) there was no significant difference between the three dosage regimens in either total or 'corrected' height reduction (fig 1).

In none of these groups did the girls develop side effects that lasted more than three months. The main side effect was nausea. Some had dysmenorrhea, but usually this disappeared after some months. A detailed report on side effects was published earlier and showed fewer problems with low dose treatment.¹³ The girls were not followed up systematically after completion of treatment. Some have become mothers and, as far as we know, none has developed infertility problems or malignant disease. This is too early to ascertain breast and genital carcinomas. No girl has developed prolactinoma to our knowledge.

Discussion

In 1975 Zachmann *et al* reported a study of 40 girls treated with a daily dosage of 0.3 mg of ethinyloestradiol.²⁰ The average reduction of final height was 4.6 cm. The reduction in the youngest group with bone age 12.1–13 years was 5.8 cm while the reduction in the group with bone age 13.1–14 years was 4.0 cm. The group with bone age 14.1–15 had a reduction of 4.5 cm. The differences were not significant, but they gave an indication that the reduction of final height was less when treatment was started after bone age of about 13 years. This corresponded to the study of Kuhn *et al* reported in 1977.²¹ They presented a study with 17 girls treated with 0.5 mg daily of ethinyloestradiol. The reduction of final height was significantly greater when treatment was started before a bone age of 12 years. The mean reduction was 8.9 cm when bone age was less than 12 years and 5.5 cm when between 12 and 13 years. There was not a statistical difference in reduction before compared with after menarche (6.4 v 5.7 cm respectively). In 1978 Bierich reported a study of 41 girls treated with 7.5 mg of

conjugated oestrogen daily.⁵ The average height reduction was 7.3 cm, but 8.3 cm when treated before menarche (mean bone age 11.8 years) and 6.8 cm when treated after menarche (mean bone age 12.9 years).

Also in 1978 Crawford reviewed different oestrogen regimens.⁷ They all showed height reductions between 3.5 and 7.3 cm. However, he did not discuss whether high or low dose regimens gave different results. In 1989 Grüters *et al* reported one of the first studies where the reduction of final height in different dosage regimens was compared.⁹ They showed that the reduction of final height was 4.9 cm in the low dose (0.1 mg of ethinyloestradiol daily) compared with 5.1 cm in the high dose (0.3–0.5 mg daily) regimen. This difference was not significant. The final height was reduced when treatment was started at a bone age less than 13 years. The groups were small ($n=44$ and $n=38$ respectively) and they were treated at two different centres.

These results are all in accordance with ours. There is no statistical difference in growth inhibiting effect between the three dosages when the duration of treatment and bone age at start of treatment are taken into account. Using 0.1 mg of ethinyloestradiol is as efficient as 0.5 mg. It has been suggested that in girls with more advanced pubertal development, a higher dosage of oestrogen should be more effective.¹² In girls with bone age ≥ 13.0 years the total height reduction was 6 mm less when given 0.1 mg daily compared with the 0.5 mg regimen, but when correlated to the treatment period there was no difference. This does not justify a higher dosage (0.5 mg) which would, with a treatment period of 2.02 years, be equivalent to a total dose of about 36 years' use of a low dose (35 µg) contraceptive pill compared with six years when treated with 0.1 mg ethinyloestradiol daily for 1.63 years. Thus irrespective of the bone age when starting treatment, low dose oestrogen treatment is as effective as high dose treatment. Furthermore early treatment, starting before bone age 12.5 years, is most effective. After bone age 13 years less benefit is obtained. There is a definite decrease in growth reducing effect when bone age is ≥ 13.0 years. The difference in reduction of final height between the two groups with bone age less than 13 years is clinically not significant, although it is statistically different due to the large number of patients.

This is the first report including more than 500 tall girls from only one centre examined and treated by the same investigator. This minimises the variations observed in height measurements, bone age estimations, height predictions, and indications of treatment.

From our study we conclude that starting treatment at a bone age of about 12.0–12.5 years, using 0.1 mg of ethinyloestradiol daily for about two years, combined with 5 mg medroxyprogesteroneacetate daily for the first 10 days of every month, will give satisfactory results with an average reduction of final height of 5.2 cm. Because of the possibility of nausea, with or without vomiting, we recommend starting treatment on a Friday to minimise loss of schooling. Such side effects are most frequent with higher

dosages. As Trygstad reported in 1986, there has not been a problem of major side effects.¹³ Whether even lower dosages (for example 35 µg daily) are equally effective should be assessed in a prospective clinical trial.

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1. Livingston J *et al* (1989) Br J Clin Pharm 27 (Suppl 1): 1095-1125

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Cyclical disturbance of diabetic control in girls before the menarche

K G E Brown, C W Darby, S H Ng

Abstract

Seven diabetic girls who presented with cyclical disturbance of diabetic control before the menarche are described. In six girls cyclical hyperglycaemia occurred and in one cyclical hypoglycaemia. The index case is described in detail, and is then included in a description of the main clinical features of all seven cases. Cyclical disturbance of diabetic control may present in diabetic girls from age 9 years onwards. Home blood glucose monitoring records may reveal cyclical disturbance, usually hyperglycaemia, and usually occurring at 21-34 day intervals and lasting for two to five days. Serious illnesses and hospital admission can be averted by educating parents to make appropriate changes to insulin regimen or diet. Our hypothesis is that the disturbance of diabetic control is caused by the onset of cyclical hormonal changes, a 'menstrual' cycle before menstruation. The precise mechanism for the changes in carbohydrate tolerance is unknown.

In adult insulin dependent diabetic women an association has been described between menstruation and disturbance of diabetic control,¹ and between menstruation and hospital admission for diabetic ketoacidosis.^{1 2} In this paper we present the case histories of seven diabetic girls who experienced cyclical disturbance of diabetic control before the menarche.

Case reports

INDEX CASE

This girl had diabetes mellitus diagnosed at the age of 7.6 years. She was well controlled on a twice daily insulin (Actrapid/Monotard, Novo Nordisk) regimen with no hospital admissions until two months after her 13th birthday, 10 months before the onset of menstruation. In December 1981 after a 12 hour history of intense thirst followed by profuse vomiting, she was admitted in severe ketoacidosis. She responded rapidly to standard treatment, a diagnosis of 'viral gastritis' was made, and she was discharged after 48 hours on her usual insulin regimen in slightly increased dose. Four weeks later she again developed a sudden onset of nausea followed by profuse vomiting. She was immediately admitted, once again in severe ketoacidosis, which responded well to standard treatment.

The possible significance of the four week interval as a cyclical hormonal event was

explained to her mother. She was advised to test the blood glucose frequently from around the 26th day after the onset of the last episode of disturbance of diabetic control, and to give extra Actrapid insulin as necessary. A pattern emerged of sudden increases in blood glucose concentrations for two days at 26 day intervals. At these times the total daily dose of insulin was increased by between 15% and 30%. This involved increasing the usual morning and evening Actrapid doses and also giving midday and/or midnight Actrapid injections as necessary, over a two day period, to control the blood glucose readings. Despite nine further episodes of cyclical diabetic disturbance, no further hospital admissions were needed. The menarche occurred in October 1982. The cyclical disturbance stopped completely and there was no hyperglycaemia in association with established periods.

CLINICAL FEATURES OF ALL SEVEN GIRLS (INCLUDING INDEX CASE)

The salient clinical features are summarised in the table. At the time of the development of cyclical diabetic disturbance, one girl was at Tanner stage 1 but the other six were in early puberty at Tanner stage 2.³ In six out of seven girls the episodes started with abdominal symptoms, vomiting in four, and abdominal pain and diarrhoea in two.

In six girls cyclical hyperglycaemia occurred and five of these girls were admitted to hospital for a total of 11 episodes of diabetic ketoacidosis. In four girls admitted to hospital with ketoacidosis the white cell count was above $15.0 \times 10^9/l$ and fever was present. However no evidence of infection was found and they recovered without antibiotic treatment.

Clinical features of seven girls with cyclical disturbance of diabetic control

	Mean	Range
Age at diagnosis of diabetes (years)	6.8	1.9-11.2
Age at development of cyclical disturbance (years)	10.8	9.7-13.2
Cycle length in days between episodes	31	21-56
Duration of cyclical disturbance (days)	3	2-5
No of cyclical episodes	18	7-40
Insulin dose during time of cyclical disturbance (U/kg body weight)	1.2	1-1.7
HbA _{1c} during time of cyclical disturbance (n=5)*	10.9	7-15.8
Insulin increase for hyperglycaemia (% of total daily dose) (n=6)	20.5	8-36
Age at menarche (n=6)	13.3	12.5-14.0
Established menstrual cycle length (days) (n=6)	31	21-56

*Excludes the first two girls who presented in 1982 before we were measuring HbA_{1c}; normal value <7.5%.

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In one girl the diagnosis was made retrospectively *after* the menarche when it became clear that established menstrual cycle length was 56 days. The unusual cycle length and intercurrent infections had confused diagnosis, but review showed a clear pattern of hyperglycaemia every two months up to the menarche.

One girl presented with relative hypoglycaemia at 26–30 day intervals. She had always had poor diabetic control with a glycated haemoglobin (HbA_{1c}) around 14% (normal <7.5%) and blood glucose concentration in the range 11–22 mmol/l. At approximately monthly intervals blood glucose dropped to around 7 mmol/l at which concentration she experienced hypoglycaemic symptoms. This was treated with extra carbohydrate without insulin reduction. She had a single hospital admission for one of these cyclical episodes, which was preceded by abdominal pain and vomiting. The admission blood glucose concentration was 4.4 mmol/l and the symptoms settled over 24 hours without special treatment or change in her usual insulin dosage.

In the six girls who have passed the menarche, disturbance of diabetic control has continued in association with menstruation in three, and has stopped completely in three. Menstrual cycle length is essentially the same as the cycle length between episodes of disturbance of diabetic control before the menarche.

Insulin requirements show no clear pattern of change. When insulin requirements between episodes of cyclical diabetic disturbance are compared with requirements one year after the menarche, in the index case there was a fall (0.4 U/kg), in two girls no change, and in four girls a small rise (0.1–0.2 U/kg). Changes in HbA_{1c} values however did show a pattern. In three girls with high values (>10%) while cyclical diabetic disturbance was still occurring, the values fell one year after the menarche to reasonable values (7.5–9%). One of these three was the girl with cyclical hypoglycaemia and very poor diabetic control between episodes. The other two had the most severe cyclical diabetic disturbance and together accounted for six hospital admissions. In two girls with reasonable HbA_{1c} values while cyclical disturbance was occurring values were unchanged one year after the menarche.

Discussion

We first observed cyclical disturbance of diabetic control early in 1982 in the index case who had a total of 11 potentially life threatening episodes. After her menarche the serious monthly episodes of hyperglycaemia stopped completely. Over the past eight years we have observed a total of seven girls with cyclical disturbance of diabetic control before the menarche. Six of the girls experienced hyperglycaemia and one hypoglycaemia. In all the girls the cyclical disturbance presented between the ages of 9 and 14 years. During the same eight year period we have cared for 52 girls from age 9 years through to either 14 years or the menarche. The incidence of this condition in our centre is therefore 13.5% of susceptible girls.

The condition should be considered in any episode of unexplained diabetic ketoacidosis, and a raised white cell count and fever do not exclude the diagnosis. Our current policy is to give education about this condition to parents of diabetic girls from age 9 years. They are advised to watch for monthly episodes of hyperglycaemia, although the possibility of hypoglycaemia is mentioned. The possibility of the diagnosis is now often first raised by parents (this has happened in four of the last five cases) and is confirmed by inspection of the home blood glucose record book, and by careful prospective testing.

The condition is managed by parents testing blood glucose concentrations frequently from two days before the expected cyclical disturbance. They also test for ketones in the urine. All girls in the susceptible age group in Bromley are on twice daily soluble/isophane insulin, usually given as a premixed insulin (for example, Humulin M3, Lilly). For the first few episodes of diabetic disturbance parents are advised to give supplementary doses of soluble insulin with the usual morning and evening insulin if blood glucose concentration rises above 15 mmol/l. They may also give extra soluble insulin before lunch and occasionally even during the night. As an initial guideline the supplementary dose of soluble insulin is based on the usual 24 hour insulin dose. If blood glucose concentration is raised above 15 mmol/l, and urine ketones are (++) or less, one tenth (10%) of the 24 hour insulin dose is given. If ketones are more than (++), 15% is given. With experience of a few cycles of diabetic disturbance the usual morning and/or evening insulin doses may also be increased, and in milder cases this may alone prove sufficient. The one girl with cyclical hypoglycaemia was managed by giving extra carbohydrate only. Reduction of insulin dosage might prove necessary if a child with more severe episodes of hypoglycaemia were to present. Our view is that the disturbance of diabetic control is associated with cyclical phenomena, similar to those occurring in the adult menstrual cycle, but preceding the menarche. The grounds for this assertion are twofold. Firstly, the cycle length of diabetic disturbance before the menarche, and the established menstrual cycle length, are identical in four cases and within two days in two cases. In this respect one girl is particularly interesting in that the condition was firmly diagnosed only in retrospect, when a 56 day menstrual cycle was established. Secondly, similar problems with diabetic control continued in association with menstruation in three cases. The seven girls described here do not differ from the rest of our clinic population in relation to overall diabetic control as reflected in HbA_{1c} measurements or insulin requirements. Poor diabetic control in three girls was in large part the result of the cyclical disturbance and the HbA_{1c} values improved after the menarche when the cyclical disturbance stopped.

We are not aware of any previous definitive description of this condition. The only record in the literature of cyclical diabetic disturbance before the menarche is in the case reported by

Hubble.⁴ He described a girl who developed diabetes at age 13 years, severe recurrent diabetic ketoacidosis from age 14.1 years, and the menarche at age 14.6 years. This was an exceptional case requiring up to 19 200 units of insulin in one day. The severe cyclical insulin resistance continued in association with menstruation and she died during an episode of diabetic ketoacidosis aged 15.1 years. This case may have been an extreme example of the condition we are describing.

In non-diabetic menstruating adult women changes in carbohydrate tolerance occur, with a tendency to hypoglycaemia in the days 1–3 before menstruation and hyperglycaemia at the onset.^{5–6} Hypoglycaemia may sometimes contribute to the premenstrual syndrome.⁷ In one study of 200 insulin dependent diabetic adult women interviewed, 53 noted hyperglycaemia, and 23 relative hypoglycaemia, in association with menstruation.¹ Menstruation has been associated with diabetic ketoacidosis leading to hospital admission.^{1–2} Recurrent diabetic ketoacidosis has also been described with each menstruation cycle,^{4,7} in one case occurring with every menstruation over one year.⁸ A detailed review of the effects of the menstrual cycle on medical disorders lists more than 100 variables that fluctuate during the menstrual cycle.⁹ With regard to diabetes and the menstrual cycle the review concludes that 'one can only speculate as to the reasons for altered diabetic control'. It is known that sex hormones can modulate insulin receptors, and binding is higher in the follicular than in the luteal phases of the menstrual cycle.⁶ It has been suggested that increased insulin binding in the follicular phase is associated with hypoglycaemia^{6,10} and decreased binding in the luteal phase is associated with impaired carbohydrate tolerance and hyperglycaemia.^{6,9} This observation might explain the cyclical hyperglycaemia in six of our cases and the hypoglycaemia observed in one of our cases.

Another possible explanation for cyclical disturbance of diabetic control is that it is associated with growth. Compared with both prepubertal children and adults, increased insulin resistance during puberty has been demonstrated in diabetic and non-diabetic children, and the response to insulin is inversely correlated with 24 hour concentrations of growth hormone.¹¹ Growth hormone surges have also been associated with the dawn phenomenon in adolescent diabetics.¹² However if growth hormone is responsible for cyclical disturbance of diabetic control one would expect to see the condition in boys, and we have not. The literature contains no data showing monthly cyclical changes in growth hormone concentrations before the menarche, and in addition concentrations do not change significantly during the menstrual cycle.¹³ Also

cyclical surges of growth hormone or other insulin antagonists would not explain cyclical hypoglycaemia. Further studies in girls with cyclical diabetic disturbance before the menarche could include ultrasound examination of the ovaries. This could establish the occurrence of cyclical follicle formation, and the relationship to the diabetic disturbance, and confirm that the disturbance is associated with a 'menstrual' cycle. Performing an euglycaemia insulin clamp procedure in mid-cycle and at the time of cyclical diabetic disturbance, together with sex hormone, gonadotrophin, and counter-regulatory hormone (growth hormone, cortisol, etc) measurement, should confirm changes in insulin resistance and might elucidate mechanisms.

Why is this relatively common cyclical disturbance of diabetic control only now being described? The first reason is the operation for the past 15 years in Bromley of a special paediatric diabetic clinic with close involvement of specialist diabetes nurses, which brings together all the district's diabetic children. The second reason relates to the introduction of frequent home blood testing in our diabetic children over the last 10–15 years. The third reason relates to the education of parents about the condition in the clinic and in a self help group which has run for 10 years.

It is important to recognise this condition, and to educate parents so that serious and life threatening disturbance of diabetic control can be prevented.

We are grateful to Lilly Industries Limited for the grant supporting one of us (CWD) for one consultant session per week in paediatric diabetes.

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Imaging in urinary tract infection

F V Gleeson, I Gordon

Abstract

The relationship of vesicoureteric reflex (VUR) and renal scarring was studied in 94 children (188 kidneys) with proved urinary tract infection in a district general hospital. There were 61 girls and 33 boys, with nine girls and 17 boys aged less than 1 year, 31 girls and nine boys aged between 1 and 5 years, the remaining 28 children were over 5 years of age. All children had a micturating cystourethrogram and a ^{99m}Tc (technetium) dimercaptosuccinic acid (DMSA) scan. Forty two of the 188 kidneys were scarred and 70 of the kidneys had VUR. Only 37.1% of the kidneys with reflux were scarred but 61.9% of the scarred kidneys had VUR. In children of less than 1 year, 48% of kidneys with VUR were scarred whereas 70.6% of scarred kidneys had reflux. In children between 1 and 5 years of age only 36.4% of kidneys with VUR were scarred but 63.2% of scarred kidneys had VUR.

There is good correlation between the detection of a scarred kidney on DMSA and the presence of vesicoureteric reflux. However the detection of reflux particularly in children over 1 year of age shows poor correlation with renal scarring. This suggests that the primary imaging in children over 1 year of age presenting with a urinary tract infection should be of the kidney: a cystogram should be performed only if the DMSA scan is abnormal.

Urinary tract infection is common in childhood with a reported incidence of 1.7/1000 boys at risk/year and 3.1/1000 girls.¹ This incidence is reversed in boys and girls under 1 year of age. Reflux nephropathy, renal damage caused by vesicoureteric reflux (VUR) plus infection, is a significant cause of end stage renal failure in young adults. It has been estimated that the risk of renal failure due to reflux nephropathy in children presenting with urinary tract infection is slightly less than 1% for boys and less than 0.5% for girls.² Hypertension is the other major complication seen in up to 13% of patients with a history of reflux nephropathy.³ An increased incidence of toxemia of pregnancy has also been reported.³ Despite the high morbidity of reflux nephropathy and the relative frequency of urinary tract infection in childhood there remains considerable controversy over how best to investigate these children.^{4 5} The age of the child when the infection occurs and its association with VUR seem the most critical factors. The kidneys of young children, less

than 1 year old, are the most vulnerable, but children over 5 years seem safe, with new scars unlikely to develop.⁶ The main debate is on the children between these two ages, those aged 1 to 5 years. In this study the relationship of the scarred kidney to VUR and VUR to the scarred kidney are assessed in these three age groups.

Patients and methods

Children presenting to Queen Elizabeth Children's Hospital, Hackney, London (QEH) with their first episode of proved urinary tract infection between September 1985 and June 1990 were selected for study. Only those children with a structurally normal renal tract were included. Additional children with neurological and skeletal abnormalities were excluded from the study.

All children underwent a micturating cystourethrogram, to assess reflux, at QEH and a ^{99m}Tc (technetium) dimercaptosuccinic acid (DMSA) renal scan, to detect renal scarring, at the Hospital for Sick Children, Great Ormond Street. The DMSA scans were performed a minimum of four weeks after the micturating cystourethrogram. Images were obtained in the posterior and both posterior oblique projections four hours after the intravenous injection of 100 MBq/70 kg with the child lying directly on the gamma camera. The results of both the micturating cystourethrogram and the DMSA scan were recorded from the patient's radiography folder.

Results

Ninety four children with 188 kidneys were eligible for analysis (tables 1 and 2). There were 42 (22.3%) scarred kidneys and 70 (37.2%) kidneys were associated with VUR. The incidence of VUR was highest in the youngest age group (48.6%), falling to 21.4% in those children

Table 1 Children grouped by age and sex

Age (years)	Girls	Boys	Total
<1	9	17	26
1-5	31	9	40
>5	21	7	28
All ages	61	33	94

Table 2 The relationship of reflux and scarring in children

	Girls	Boys	Total
Scarring detected	20	15	35
Reflux detected	29	21	50

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Table 3 The relationship of reflux to scarring

	No of kidneys with VUR	DMSA scan	
		Scarred	Normal
All children:	70	26	44
Boys	30	10	20
Girls	40	16	24
Age (years):			
<1	25	12	13
1-5	33	12	21
>5	12	2	10

Table 4 The relationship of scarring to reflux

	No of kidneys with scarring	Micturating cystourethrogram	
		With reflux	Without reflux
All children:	42	26	6
Boys	17	10	7
Girls	25	16	9
Age (years):			
<1	17	12	5
1-5	19	12	7
>5	6	2	4

over 5 years of age in keeping with the natural history of reflux. Only 37.1% of the kidneys associated with reflux were scarred if all ages are considered. In children under 1 year of age this increased to 48.0% but fell to 36.4% in those aged between 1 and 5 years. Only 16.7% of kidneys associated with VUR in those over 5 years were scarred (table 3).

Renal scars were detected in 42 (22.3%) of the 188 kidneys studied. Of all the scarred kidneys, VUR was seen in 26 (61.9%). In children less than 1 year of age with renal scarring VUR was seen in 70.6%. In children aged between 1 and 5 years with renal scarring, VUR was seen in 63.2% (table 4).

The prevalence of both VUR and renal scarring declined with increasing age.

Discussion

The long term morbidity associated with reflux nephropathy is due to the presence of renal scarring. This requires clinicians both to attempt to prevent it and to identify those children already affected at presentation. The majority of children with reflux nephropathy are noted to have scarred kidneys at the time of investigation of their initial urinary tract infection.⁶ Longitudinal studies have mostly failed to demonstrate the development of renal scars not present on first investigation in children followed up for urinary tract infection.⁷ The Birmingham Reflux Trial confirmed that although it is possible to stop reflux with surgery, there is no apparent advantage regarding renal scarring, breakthrough infection, or renal function when compared with non-operative treatment, thereby casting doubt on the benefit of its detection.⁶

Renal scars may be detected by intravenous urography, ultrasound, or DMSA isotope scans. Ultrasound is the least and DMSA the most sensitive technique.⁸⁻¹⁰ DMSA may in fact be over sensitive if performed within four weeks of the urinary tract infection, detecting transient areas of abnormality that may not develop into scars on long term follow up.⁹ Intravenous urography is difficult to perform in young children and has been shown to be insensitive when compared with DMSA scans particularly in children aged less than 6 years.⁹

This study confirms previous reports of the incidence of VUR in children presenting for investigation of a urinary tract infection.¹¹ The high incidence of scarring (48%) associated with reflux in the children under 1 year of age supports the argument that the young child, less than 1 year old, is the most susceptible to reflux nephropathy. Both clinicians and radiologists feel that this age group should undergo both cystography and DMSA investigations at presentation.

However in children over 1 year of age VUR not associated with scarring is seen in 65% of cases, thus a kidney associated with reflux in this age group is more likely to be normal than scarred. If the initial imaging is directed at the kidney in the child over 1 year of age then 56% of scarred kidneys were shown to have VUR. If this policy is assessed in those aged 1 to 5 years this then increases to 63%.

We believe that renal scars detected by a DMSA scan are a good predictor of reflux in the child over 1 year of age. VUR in the older child should not be regarded as the 'villain of the piece' rather interest should be focused on the kidney which if scarred would direct the clinician to exclude VUR.

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Covert bacteriuria: long term follow up

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Abstract

In a longitudinal prospective study 58 school-girls with covert bacteriuria were followed up for an average of 11.2 years (range 8.8 to 13.5 years). Intravenous urography was carried out at the start of the study (aged 4 to 11 years) and after completion of the follow up period (aged 14.8 to 22.3 years). After random allocation 27 of these girls received intermittent treatment for covert bacteriuria for the first four years and the control group received no treatment. The effect of covert bacteriuria, treatment, vesicoureteric reflux, and reflux nephropathy at presentation on the final renal length, progression of scarring, and development of new scars was analysed. No new scars were found in girls with bilaterally normal kidneys. In girls with reflux nephropathy, three kidneys showed progression of existing scars and two kidneys developed new scars. It was shown that final renal length was not influenced by vesicoureteric reflux or treatment, but reduced renal length at final assessment was associated with the presence of kidney scarring at initial assessment.

Normal kidney growth has been considered to be an index of well being of the kidney whereas poor growth has been associated with renal disease. Aperia *et al* have shown that kidney size is closely related to glomerular filtration rate in children with reflux nephropathy.¹ It has been suggested that bacteriuria and vesicoureteric reflux inhibit renal growth as well as causing renal scarring, but there is little evidence to support this. The aim of treatment in asymptomatic individuals is to prevent renal damage. Previously studies in schoolgirls with covert bacteriuria showed that vesicoureteric reflux is present in 25%-33%.²⁻³ Reflux nephropathy is an important cause of severe hypertension in children⁴ and accounts for at least 10% of cases of end stage renal disease.⁵ This study has assessed the long term effect of covert bacteriuria, vesicoureteric reflux, and treatment on renal growth in asymptomatic individuals with normal kidneys and those who had evidence of reflux nephropathy at the outset of the study.

Patients and methods

SUBJECTS AND OUTLINE OF THE STUDY

The subjects of this study were 58 females who had been identified while at primary school, aged 4 to 11 years, during a screening programme for bacteriuria.⁶ The outline of the study is shown in table 1. The distribution of

initial radiological findings and prevalence of infection at the time of final intravenous urogram is shown in table 2. After the initial radiological investigations girls were randomly allocated to control or treatment groups. Twenty seven girls were in the treatment group and received short courses of appropriate antibiotics according to the results of urine culture and antibiotic sensitivity of infecting organisms. After four years of follow up the controlled trial was discontinued. Subsequently long term low dose prophylaxis with trimethoprim or nitrofurantoin 1-2 mg/kg at night was offered to 12 girls who had scarred kidneys and continued infection. This was taken for less than 12 months by 10 girls and for three and four years by the remaining two girls. The two girls who took long term treatment continued to have break through infections.

RADIOLOGY

Intravenous urography was carried out at the start and after an average of 11.2 (range 8.8-13.5) years of follow up and micturating cystourethrography at the start only, using the techniques previously described.³ All radiographs were reviewed separately by two teams of two observers for the presence or absence of scarring and on the final radiographs for the development of new or progressive scars. Each kidney was measured as well as the distance between the superior border of the first lumbar vertebra and inferior border of the third lumbar vertebra (L1-L3 height) as has been described by Eklof and Ringertz.⁷ Whenever there was a discrepancy in renal length or vertebral height

Table 1 Outline of the study

No of girls screened	13369
No (%) with bacteriuria detected	207 (1.6)
No undergoing IVU initially	180
No completing four year follow up and IVU	167
No (%) completing 11 year follow up and IVU	58 (32)

IVU=intravenous urography.

Table 2 Distribution of initial radiological findings in 58 girls and prevalence of infection at time final intravenous urography (IVU) performed

Initial radiological findings	No of girls	Prevalence of infection when final IVU performed (%)
Scarred kidney(s) with reflux	14	29
Scarred kidney(s) without reflux	7	29
Normal kidneys with reflux	9	22
Normal kidneys without reflux	28	32

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of more than 5 mm or a discrepancy in observation of scarring the radiographs were reviewed by all four observers and agreement was reached in every case. Renal length and L1-L3 height have been taken as the mean of the two sets of observations, and kidney length expressed as a proportion of vertebral height. The grade of vesicoureteric reflux has been classified I to III as recommended by the Medical Research Council Bacteriuria Committee. The distribution of initial radiological findings in 116 kidneys (58 subjects) is shown in table 3. The effect of vesicoureteric reflux and treatment on renal length was assessed for bilaterally normal kidneys, scarred kidneys, and kidneys opposite scarred kidneys (hypertrophied kidneys). The effect of bacteriuria on renal length in girls with bilaterally normal kidneys was assessed by plotting renal length on centile charts relating renal length to the height of the individual (Hodson *et al*⁸).

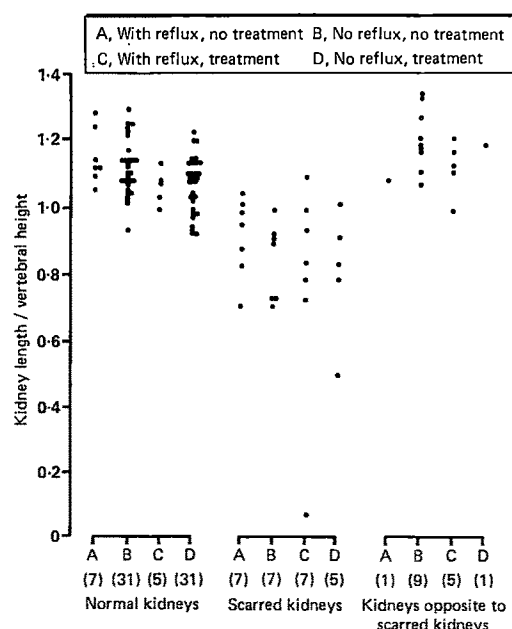
STATISTICAL ANALYSIS

The influence of vesicoureteric reflux, scarring, and treatment jointly and relatively on renal length was evaluated in a three way analysis of variance model, using the average of the lengths of the two kidneys to characterise the subject. This strategy was adopted in order to avoid the analysis being invalidated by non-independence. It was verified that the adjusted means closely correspond to what would be obtained in an analysis using the individual kidney as a unit.

Results

All of the 58 females (14 girls 14.8–17.9 years and 44 women 18.0–22.3 years) were clinically well at the time of the final follow up. Although 11 women had episodes of high blood pressure recorded, none had sustained hypertension (greater than 140/90 mm Hg) or were on anti-hypertensive medication.

Ten women had been pregnant (12 pregnancies), seven had had one live birth each, one had had two pregnancies and two live births. There had been two terminations and one spontaneous abortion. (One woman had had a termination followed by a live birth.) Information on bacteriuria was available in the nine successful pregnancies and asymptomatic bacteriuria was documented in three. One of



Effect of treatment and vesicoureteric reflux on final renal length in bilateral, normal kidneys and normal kidneys opposite to scarred kidneys, as assessed by ratio of kidney length/vertebral height (cm/cm). (The number of kidneys in each group are shown in parentheses.)

these women later developed symptoms of acute pyelonephritis.

No new scars developed in girls with bilaterally normal kidneys. New scars were seen in two kidneys (one normal kidney opposite to a scarred kidney and the other already scarred) both of which were drained by ureters with grade III vesicoureteric reflux. Three kidneys showed progression of scarring, all of which had refluxing ureters (grade I in one and grade III in two kidneys). One woman had a 5 mm renal calculus in a normal kidney and another had renal calcification in the scarred lower pole of a refluxing duplex system. Two women with scarred kidneys developed caliceal cysts. The effect of treatment and vesicoureteric reflux on final renal length is shown in the figure. There was no evidence that bacteriuria was associated with a reduction in final renal length in women with radiologically normal kidneys. Although scarred kidneys were significantly smaller than normal kidneys ($p < 0.001$), no effect of vesicoureteric reflux or treatment was demonstrated.

Discussion

The results of this study support the findings of the previous study (after four years of follow up) that new scars do not develop in girls with bilaterally normal kidneys.⁹ The two women who developed new scars and the three women who had progression of existing scars already had evidence of scarring and vesicoureteric reflux. While it is possible that progression of scarring in these three women might have been prevented by long term low dose prophylaxis or surgery, the benefits of these forms of intervention are not proved. The Birmingham Reflux Study Group showed that a significant number of children developed progressive scarring despite long term prophylactic antibiotic

Table 3 Distribution of initial radiological findings in 116 kidneys

Initial radiological findings	No of kidneys
Bilateral normal kidneys with reflux	12 { Grade I 5 Grade II 3 Grade III 3
Bilateral normal kidneys without reflux	62
Scarred kidneys with reflux	14 { Grade I 5 Grade II 3 Grade III 6
Scarred kidneys without reflux	12
Normal kidneys (opposite a scarred kidney) with reflux	6 { Grade I 0 Grade II 4 Grade III 2
Normal kidneys (opposite a scarred kidney) without reflux	10

treatment or surgery.¹⁰ Women with covert bacteriuria, many of whom have never had clear symptoms of urinary tract infection, are poorly motivated to comply with inconvenient or painful treatment.

In addition to renal scar formation urinary tract infection may interfere with renal growth.^{11 12} We have shown that scarred kidneys grow significantly less well than normal kidneys ($p < 0.001$) but we, like Claesson *et al*,¹³ have been unable to demonstrate a detrimental effect of reflux or covert bacteriuria on renal growth. The final renal length of bilaterally normal kidneys with or without vesicoureteric reflux was normal even after prolonged exposure to bacteriuria.

This study has shown that the prevalence of reflux nephropathy in schoolgirls with covert bacteriuria does not change after 4 years of age. In some girls (24% in this study) reflux nephropathy is a slowly progressive disease. However in the absence of scarring, covert bacteriuria is benign and does not affect renal length, even if vesicoureteric reflux is present, after 4 years of age. Although further studies are required to show the best way to prevent progressive damage in girls with established scarring and persisting reflux, it is clear that the only way to reduce the prevalence of reflux nephropathy is to improve the diagnosis and treatment of infants and very young children under 4 years of age.

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Urinary tract infection in febrile convulsions

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Abstract

A retrospective review of the casenotes of 403 children admitted to hospital with febrile convulsions was performed to estimate the frequency of symptomatic urinary tract infection and examine medical practice in making this diagnosis. A total of 228 (56%) children had urine cultured: 150 bag specimens, 76 clean voided samples, and two suprapubic aspirates. There were 13 'probable' and six 'possible' infected urine samples together representing 5% of the whole study population ($n=403$), 8% of those having urine cultured ($n=228$), and 12% of those providing uncontaminated urine samples ($n=155$). Those with first febrile convulsions and those aged under 18 months were more likely to have urine examined. Practices varied significantly between different hospitals. These results suggest that there has indeed been a need for practice guidelines, and that further audit of practice is required to assess their impact.

The lack of a universal policy in the management of urinary tract infection in childhood has been recognised in a recent report from the Royal College of Physicians (RCP).¹ Recommendations were made regarding management, research, and audit. In particular the early diagnosis and treatment of urinary tract infection in febrile children with possible concomitant illness was emphasised. This is important as urinary infection in early childhood may cause renal scarring, especially if there is a delay in treatment. This may lead to later hypertension, reduced glomerular filtration rate, and renal failure.²⁻³ In women it may lead to pregnancy induced hypertension and complicated delivery.⁴ Vesicoureteric reflux may be present in a third of infants with urinary tract infection and has implications for other family members also.⁵

There is, therefore, a serious penalty for failing to diagnose and treat urinary tract infection. At the same time a false positive diagnosis will unnecessarily subject a healthy infant to inappropriate investigations including micturating cystourethrography. For these reasons it is essential to develop policies that facilitate early and accurate diagnosis. This study was carried out before the RCP report and aimed to assess the local paediatric approach to establishing, or excluding, the diagnosis of urinary tract infection in a group of febrile children with convulsions. At the same time an estimate of the frequency of urinary tract infection in this population would give an indication of the size of the problem. This

group was chosen because of its close correspondence to the age group at greatest risk of developing renal scarring and because fever is the commonest, and possibly most significant, symptom in infants and young children with urinary tract infection.⁶

Patients and methods

Data were collected by retrospective analysis of casenotes of children under 6 years old admitted to three hospitals in South Glamorgan with a diagnosis of febrile convulsion. Cases were identified through the Hospital Activity Analysis during the period 1 January 1986 to 31 December 1987. The notes were examined for evidence of fever, details of the fit, the child's medical history, the cause of fever, types of investigation performed, and for evidence of exclusion of urinary tract infection.

STATISTICS

The data were processed using a VAX 8530 computer to generate frequency distributions and results compared using the χ^2 test.

DEFINITIONS

Febrile convulsion included any ictal episode, simple or complex, of any duration associated with a febrile illness from the history. A simple febrile convulsion was defined as a generalised convulsion, not focal, lasting less than 15 minutes with no neurological sequelae and occurring only once within 24 hours. A complex convulsion was any other fit.⁷ Probable urinary tract infection was diagnosed when a pure growth of greater than 10^5 colony forming units (cfu)/ml was obtained. Possible urinary tract infection was diagnosed when a pure growth of a single organism between 10^4 and 10^5 cfu/ml was obtained.

Urine samples showing a mixed growth of organisms more than 10^3 cfu/ml were deemed to be contaminated and urine samples which grew less than 10^3 cfu/ml were considered to be sterile.

Results

During the 24 month period studied there were 13 801 paediatric medical admissions to the three hospitals in South Glamorgan of which 432 (3.1%) were attributed to febrile convulsions. Notes were retrieved for 403 (93%); there were 169 girls (42%) and 234 boys (58%) with a mean age of 24 months (range 1-71 months).

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Altogether 252 admissions were for first convulsions; 110 had complex fits; 31 children had abnormal neurological findings or developmental delay. There were 185 episodes of first time, simple, febrile convulsions in children with normal neurology having a recorded fever of 37.5°C or greater. There was no seasonal variation in admission rate.

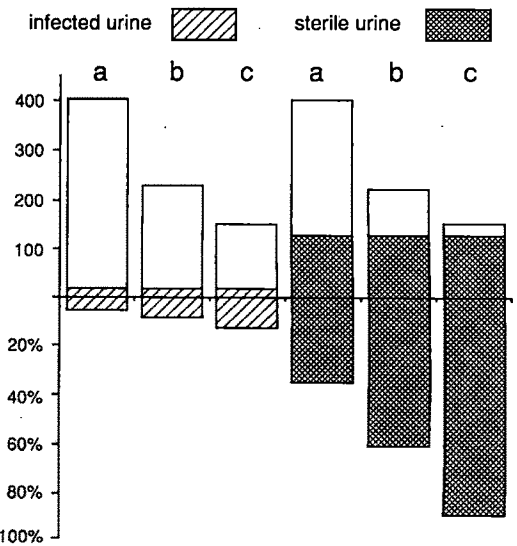
One hundred and ninety one children underwent blood tests which included white cell count, haemoglobin, glucose, calcium, urea and electrolyte concentrations, virological studies and blood culture. One hundred and thirty two children had radiography of the chest and/or skull. Swabs were taken from the ears, nose, throat, or skin in 182 children; 65 children had cerebrospinal fluid examined.

A total of 228 urine samples were cultured: 150 (66%) were collected into sterile plastic bags; 76 (33%) were clean voided or midstream samples; and two (1%) were collected by suprapubic aspiration.

Table 1 shows the clinical diagnoses made at discharge. Table 2 shows the results of urine culture. Urine samples were contaminated in 56 of 163 (34%) bag specimens and 17 of 86 (20%) of clean voided samples. Twenty six of 112 girls (23%) and 47 of 150 boys (31%) provided contaminated samples and 56 of the 73 contaminated samples (77%) were from children under 24 months. The two suprapubic aspirates were sterile. Table 3 shows clinical details and results of urine culture and microscopy in the children with urinary tract infection: 13 'probable' and six 'possible'. The figure displays the frequency of urinary tract infection which varies according

Table 1 Discharge diagnoses made by clinicians to account for febrile convulsion

Diagnosis	No of cases
Upper respiratory tract infection	97
Tonsillitis	76
Otitis media	47
'Viral illness'	30
Gastroenteritis	19
Chest infection	15
Urinary tract infection	7
Chickenpox	7
Measles	7
Bacteraemia	5
After vaccination	4
Mumps	2
Encephalitis	2
Abscess	1
Meningitis	1
Blocked ventriculoperitoneal shunt	1
None	82
Total	403



Numbers (above line) and percentages (below line) of infected and sterile urine samples in relation to (a) whole group (n=403), (b) those children in whom urine was cultured (n=228), and (c) those children in whom the urine was not contaminated (n=155).

to the reference group. The mean age was 22 months (range 7–54 months) with seven boys and 12 girls. *Escherichia coli* was the infecting organism in 84% of cases. Children under 18 months ($\chi^2=8.31$, $p<0.001$), those having their first fit ($\chi^2=23.95$, $p<0.001$), and children having one or more other tests performed ($\chi^2=62.6$, $p<0.001$) were more likely to have urine cultured. There were also significant differences between all three hospitals with 74%, 59%, and 42% of admissions respectively having urine examined and cultured ($\chi^2=23.86$, $p<0.001$). Urine culture was not influenced by sex, developmental delay, type of seizure, or presence of an obvious cause for the fever.

Discussion

The need to consider the diagnosis of urinary tract infection in every febrile infant or young child has been emphasised by the report from the RCP.¹ This is important for several reasons. First, urinary tract infection in infancy and

Table 2 Results of urine culture

	No (%) total study population (n=403)	No (%) with first, simple febrile convulsions* (n=185)
Urine examined	228 (56)	116 (63)
Urine not examined	175 (44)	69 (37)
Total urinary tract infection	19 (5)	9 (5)
Probable	13 (3)	6 (3)
Possible	6 (2)	3 (2)
Sterile urine	136 (34)	73 (39)
Contaminated urine	73 (18)	34 (18)

*These children had normal neurology.

Table 3 Characteristics of children with probable and possible urinary tract infection

Case No	Sex	Age (months)	Organism	Growth (cfu/ml)	Microscopy*	Sample type	Repeat sample
1	F	7	<i>E coli</i>	>10 ⁵	10	Bag	No
2	F	54	<i>E coli</i>	>10 ⁵	40	Clean void	Yes
3	F	16	<i>E coli</i>	>10 ⁵	50	Bag	After treatment
4	F	26	<i>E coli</i>	>10 ⁵	0	Clean void	No
5	M	18	<i>Pseudomonas</i> sp	>10 ⁵	0	Bag	No
6	F	13	<i>E coli</i>	>10 ⁵	10	Bag	Yes
7	M	8	<i>E coli</i>	>10 ⁵	50	Bag	Yes
8	F	12	<i>E coli</i>	>10 ⁵	30	Bag	Yes
9	M	15	<i>E coli</i>	>10 ⁵	Not known	Bag	No
10	F	12	<i>E coli</i>	>10 ⁵	Not known	Bag	After treatment
11	F	26	<i>E coli</i>	>10 ⁵	Not known	Bag	No
12	F	31	<i>Streptococcus faecalis</i>	>10 ⁵	0	Bag	No
13	F	42	<i>E coli</i>	>10 ⁵	100	Clean void	No
14	M	37	<i>E coli</i>	6×10 ⁴	0	Clean void	No
15	M	25	<i>E coli</i>	6×10 ⁴	0	Bag	No
16	F	9	<i>E coli</i>	6×10 ⁴	0	Bag	No
17	M	16	<i>Proteus</i> sp	6×10 ⁴	0	Bag	No
18	M	16	<i>E coli</i>	6×10 ⁴	0	Bag	No
19	F	45	<i>E coli</i>	6×10 ⁴	0	Clean void	No

*White blood cells/high power field.

Table 4 Studies of symptomatic urinary tract infection in children

Author(s)	Type of study	Age of population	Setting	No of children studied	Incidence of urinary tract infection (%)
North (1963) ¹⁶	Prospective	0-13 years	Hospital	82	3-6
Leape and McEachen (1974) ¹⁷	Prospective	?	Outpatient	156	19
Roberts <i>et al</i> (1983) ¹⁸	Prospective	0-2 years	Collaborative, hospital	501	4.1
Krober <i>et al</i> (1983) ¹⁹	Prospective	Under 3 months	Hospital	182	11
Bauchner <i>et al</i> (1987) ²⁰	Prospective	0-5 years	Outpatient	664	1.7
Bonadio (1987) ²¹	Retrospective	0-1 year	Hospital	265	5.5

early childhood often gives rise to fever but rarely gives rise to localising symptoms.⁶ Secondly, appropriate antimicrobial treatment to alleviate symptoms is unlikely to be given unless the correct diagnosis has been made. Thirdly, delays in diagnosis will not only prolong the duration of symptoms but also increase the risk of acquired renal scarring.⁸ Finally, there may be an underlying abnormality such as obstruction or vesicoureteric reflux,⁹ which increases the risk of recurrence of infection as well as the risk of acquired renal scarring.¹⁰ Such lesions will only come to light if appropriate investigation including ultrasound of the kidneys and micturating cystourethrography are later carried out.

Appropriate management with antibiotic prophylaxis and surgery¹¹ combined with parental counselling on the symptoms and management of recurrent infection have an important part to play in minimising the risk of further acquired renal damage. Furthermore, the fact that renal damage and severe systemic illness develop most often in the youngest children,¹² the group in whom localising symptoms are invariably absent, means that it is particularly important to culture urine in infancy. Unfortunately the collection of urine for culture from young children before the age of toilet training is difficult and time consuming and there is a high contamination rate, particularly when plastic collecting bags are used.¹³ The more reliable methods, catheterisation and suprapubic aspiration, are more invasive and also have disadvantages. After catheterisation there is a significant risk of developing infected urine unless antibiotics are given prophylactically and the risk of having a negative tap on suprapubic aspiration deters some doctors from routine use of this procedure.

Much of the work on the significance of the colony count was done by Kass who studied asymptomatic pregnant women and outlined criteria that would give a low risk of false positive results.¹⁴ Work in children suggests that lower counts may be indicative of infection.¹⁵ In view of the risk of renal damage if there is a delay in treatment it is more important to reduce the chance of false negative results. However, many laboratories use the same criteria for reporting infection in all age groups. For these reasons many paediatricians rely heavily on the presence of organisms and pus cells on direct microscopy for the initiation of treatment, adjusting the antibiotic if necessary when culture results are available. Difficulties arise when a contaminated sample is reported or where the results of culture are not in agreement with the diagnosis made at microscopy.

In this study, the proportion of children detected with bacteriuria was between 5% and 12%. The true proportion is dependent on the number of false negative and positive results and the number of children in whom urine was not cultured but who nevertheless had undetected urinary tract infection (see figure). These results are comparable with those of other studies (table 4¹⁶⁻²¹). The absence of an increase in the first six months of life in this study is likely to be due to the small number of infants of this age developing febrile convulsions. The use of antiseptic in some studies to wash the perineum may have the effect not only of lowering the contamination rate but also of masking true infection by inhibition of bacterial growth.²⁰

This study has confirmed the importance of urinary tract infection as a cause of systemic febrile illness in early childhood even in the absence of localising symptoms. It has also shown that paediatricians did not have a consistent policy to establish or exclude the diagnosis of urinary tract infection in every febrile child. The discovery that there were significant differences between the three hospitals in South Glamorgan suggests that local opinion is an important factor influencing paediatric practice. The limitations of urine culture with unacceptably high contamination rates, particularly in young children, suggest that greater reliance should be put on urine microscopy and that paediatricians should be more willing to collect urine by suprapubic aspiration in infants with unexplained fever. Smyth *et al* had previously pointed out inconsistencies amongst paediatricians in their investigation and long term management of childhood urinary tract infection. The RCP's guidelines have provided the impetus for further research and audit and should eventually lead to more satisfactory medical practice in this important area. Its impact must be evaluated critically in the future by further studies.

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Infant feeds: the oops factor

The oops factor must be one of the most frequent of historical regulators. It is a prime cause of wars, disasters, plague, and famine. Fairly recent memory serves to show that it may bring about the demise of prime ministers, ensures a rapid turnover of cabinet and lesser ministers, has forced the resignation of one US president, and has been prominent in the administrations of at least two others. In medicine there is the grand international oops factor such as leads to babies being born without limbs or people dying of AIDS and there are the local and personal oops potentials we all battle with from day to day. (In one respect clinical audit is a procedure for the avoidance or modification of oops.) Infant formula feeding is a procedure replete with oops potential, so much so that the manifest safety of most infant formulas must be a source of considerable relief (phew! factor). Notable oops outbreaks have given rise to pyridoxine deficiency in the 1950s, and phosphate and solute overload in the 1960s and 70s.

Between March 1978 and August 1979 two soy based formulas marketed in the US and one in Spain were grossly lacking in chloride. Babies fed on these formulas fed poorly, failed to thrive, became weak and lethargic, vomited, and developed a metabolic alkalosis with a low serum chloride and potassium. When given extra chloride they rapidly recovered from their acute illness.¹

Reports of follow up of some of these children have shown cognitive and language impairments. Now Thomas Kaleita, Marcel Kinsbourne, and John Menkes (*Developmental Medicine and Child Neurology* 1991;33:626-35) have described a distinctive syndrome of cognitive and behavioural impairments in 11 of 13 children. All children were seen because of parental concern about their development after they were fed on the chloride deficient milk and when examined they were aged 5 to 10 years. Two children had global cognitive impairment. The 11 were all of normal overall intelligence but showed an expressive language disorder, 'attention deficit hyperactivity disorder', and visual-motor, and fine motor problems. This grouping of features is unusual in other children with cognitive and behavioural deficiencies.

Makes you think, doesn't it?

ARCHIVIST

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PS. See also Michael H Malloy and colleagues. *Pediatrics* 1991;87:811-22.

Maternal and fetal influences on blood pressure

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Abstract

To study maternal and fetal influences on blood pressure in childhood 405 children aged 4 years who were born and still resident in the Salisbury health district were visited at home for blood pressure and growth measurements. Information on the pregnancy, delivery, and baby was abstracted from the routine obstetric notes.

Similar to recent findings in adults, the child's systolic pressure was inversely related to birth weight and positively related to placental weight. Systolic pressure at 4 years increased by 1.2 mm Hg for every SD decrease in the ratio of head circumference to length at birth, and by 1.1 mm Hg for every SD decrease in ponderal index at birth. Mothers whose haemoglobin concentrations fell below 100 g/l during pregnancy had children whose systolic pressures were on average 2.9 mm Hg higher than the children of mothers with higher haemoglobin concentrations.

Patterns of placental weight, birth weight, head circumference, and length that are associated with high blood pressure in adults are also associated with higher blood pressure in 4 year old children. Identification of the intrauterine influences that lead to these patterns of fetal growth could lead to the primary prevention of hypertension.

Recent findings suggest that adult hypertension originates in fetal life.^{1 2} In a study of 50 year old men and women in Preston, England, systolic and diastolic pressure were strongly predicted by birth weight and placental weight, which had independent and opposing effects.² Mean systolic pressure fell by 11 mm Hg as birth weight increased from less than 2475 g to more than 3375 g and rose by 15 mm Hg as placental weight increased from less than 450 g to more than 675 g. The highest pressures and risk of hypertension were among people who had been small babies with large placentas.² These associations, which were highly significant, were independent of gestational age, current body mass index, and alcohol intake.

These findings raise the question of whether the opposing relations of blood pressure with birth weight and placental weight are apparent in children today, and if so what is the timing and nature of the intrauterine influences. To examine this we have measured the blood pressures of 405 children, aged 4 years, born in a city in southern England, and related them to measurements at birth.

Methods

All singleton children born in hospital in the Salisbury health district between July 1984 and February 1985, and still resident in the district at the age of 4 years, were eligible for inclusion in the study. (All hospital deliveries in this health district are at a single hospital.) Four hundred subjects was estimated as the sample size needed to give 95% power to detect a difference in systolic pressure of 4 mm Hg between two subgroups of equal size, using a test at the 5% level.

Information on the pregnancy and measurements at birth was abstracted from the haematology and maternity records, including parity, first and maximum systolic and diastolic blood pressures recorded, routine haematology, gestation (estimated from the last menstrual period or, if absent, ultrasound scan), birth length, weight, head circumference, and placental weight.

Children were visited at home by one of two field workers: neither had seen the obstetric data. The children's ages ranged from 4.0 to 4.9 years (median 4.2 years): 93% were visited between the ages of 4 and 4.5 years. The child's social and medical history was recorded on a questionnaire. Social class was allocated according to occupation of the father, or if absent, the mother.³ Members of the armed forces and housewives were not allocated to a social class. The blood pressure, height, and weight of the child and both parents were measured. After the subjects had rested for five minutes, blood pressure was measured on the left arm at the level of the heart, using an automated blood pressure recorder (Dinamapp model 18465X). Cuff size was chosen according to recommendations based on those of the American Heart Association⁴: three measurements were taken at one minute intervals. Weight was measured on digital scales to the nearest 0.1 kg. Height was measured in the Frankfurt plane on a portable stadiometer to the nearest mm. Before starting the study, the procedures for measurements were standardised and the fieldworkers trained. No important interobserver variation was found during checks at intervals throughout the study, in which repeat measurements were made on subjects selected from outside the study population.

Results

Of 638 eligible children, 206 (32%) could not be traced at their last known address, or their parents did not reply to the letters of invitation, and 20 (3%) declined to take part in the study.

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Seven children reported as having renal or cardiac disorders or other congenital abnormalities were excluded. There remained 405 mothers and children, 205 boys and 200 girls. Of these 395 (98%) had haematological records and 376 (93%) had obstetric information, although this was not complete in all cases. Altogether 347 (86%) fathers were studied: 37 fathers (9%) had never or no longer lived in the same household, 10 (2%) were working away, and 11 (3%) did not wish to participate.

The children's systolic pressure fell by a mean of 5.5 mm Hg (95% confidence interval (CI) 4.2 to 6.9) from the first to the third reading. The within child SD was 9.2 mm Hg. We present the analysis of the average of the three systolic pressure measurements. Neither age or sex of child, room temperature, month and time of day, or time since last meal, had a consistent effect on mean systolic pressure. The mean systolic pressure and weight at 4 years, and the mean gestation, placental weight, and size at birth are given in table 1.

SIZE AT BIRTH, PLACENTAL WEIGHT, GESTATION, AND WEIGHT AT 4 YEARS

Placental weight and weight, length, and head circumference at birth were adjusted for gestational age by linear regression. The simultaneous effects of weight at 4 years and adjusted birth weight and placental weight on systolic pressure were examined by multiple regression (table 2). Variables were grouped into approximate fourths so that we could explore non-linear variation of systolic pressure with each variable. The lowest fourth was set as the baseline and the systolic pressure in each group is given as its difference from this. Systolic pressure rose with increasing weight at 4 years with a pronounced rise in the heaviest group. Pressure fell with increasing birth weight and rose with placental weight: the average systolic pressure in children whose birth weight exceeded 3600 g was 2.6 mm Hg (95% CI -0.8 to 6.0) below that of children whose birth weights were 3000 g or less. Children whose placental weights were greater than 750 g had average pressures of 2.6 mm Hg (95% CI -0.8 to 6.0) above those whose placental weights were 550 g or less.

We further examined the association of systolic blood pressure with size at birth by analysing length and head circumference at birth after adjustment for gestational age. Children whose head circumferences had been in the lowest fourth (≤ 33.5 cm) had pressures which were 1.3 (95% CI -2.1 to 4.7) mm Hg above those whose head circumferences had been in the highest fourth (> 35.5 cm). Children

Table 2 The simultaneous effects of weight at 4 years, birth weight,* and placental weight* on systolic pressure, expressed as mean difference (95% CI) from the baseline

	No	Systolic pressure (mm Hg)
Weight at 4 years (kg):		
≤16.5	108	0.0 (baseline)
-17.5	92	0.1 (-2.6 to 2.9)
-18.5	66	0.3 (-2.7 to 3.4)
>18.5	98	3.7 (0.8 to 6.5)
Birth weight (g):		
≤3000	75	0.0 (baseline)
-3300	102	-0.8 (-3.7 to 2.2)
-3600	82	-0.9 (-4.1 to 2.4)
>3600	105	-2.6 (-6.0 to 0.8)
Placental weight (g):		
≤550	96	0.0 (baseline)
-650	102	-0.1 (-3.0 to 2.7)
-750	83	0.6 (-2.5 to 3.7)
>750	83	2.6 (-0.8 to 6.0)

*Birth weight and placental weight are adjusted for gestational age.

whose lengths had been in the lowest fourth (≤ 49.5 cm) had pressures that were 1.4 (95% CI -1.8 to 4.6) below those whose lengths had been in the highest fourth (> 52.5 cm). Because of the opposing relations of systolic pressure to head circumference and length, mean systolic pressure rose as the ratio of head circumference to length decreased. A decrease in the ratio of 1 SD (0.03) was associated with a 1.2 mm Hg (95% CI 0.1 to 2.2) increase in systolic pressure. We examined the relations of systolic pressure to birth weight and length using the ponderal index (weight/length³). Systolic pressure fell as the ponderal index at birth increased. An increase in ponderal index of 1 SD (3.1 kg/m³) was associated with a 1.1 mm Hg (95% CI 0.1 to 2.1) decrease in systolic pressure.

MATERNAL BLOOD PRESSURE, HEIGHT, HAEMOGLOBIN CONCENTRATION, AND SMOKING

The mean (SD) systolic pressure of mothers, measured when the child was aged 4 years, was 120.1 (13.5) mm Hg. The children's mean systolic pressure rose as the mother's systolic pressure increased (table 3). There was a similar relation with the mothers' maximum systolic pressure during pregnancy. As would be expected the mothers' blood pressure at the time of the survey and during pregnancy were strongly related.

Table 3 shows the relation of maternal variables to the children's systolic pressure which is given both unadjusted and adjusted (by linear regression) for its two main correlates, child's weight and mother's systolic pressure. The mean (SD) maternal height was 162.6 (5.9) cm. Although the children of the smallest

Table 1 Characteristics of the sample by sex

	Boys		Girls	
	No	Mean (SD)	No	Mean (SD)
Birth weight (g)	205	3391 (576)	200	3342 (495)
Placental weight (g)	185	662 (192)	181	653 (149)
Length at birth (cm)	181	51.5 (2.6)	180	50.8 (2.4)
Head circumference at birth (cm)	183	34.8 (1.4)	182	34.3 (1.4)
Gestation (weeks)	205	40.1 (1.7)	198	40.2 (1.6)
Weight at 4 years (kg)	205	17.8 (2.2)	200	17.3 (2.2)
Systolic blood pressure (mm Hg)	205	105.7 (9.7)	200	105.0 (9.9)

mothers had the highest pressures, there was no overall trend with mother's height (table 3).

We examined the lowest haemoglobin concentrations and mean corpuscular volumes for each mother during pregnancy. We defined anaemia by a commonly used clinical definition of a haemoglobin value below 100 g/l. We also divided haemoglobin concentrations at 110 g/l; this is the World Health Organisation's (WHO) defining concentration for pregnancy anaemia.⁵ The children of anaemic mothers (haemoglobin below 100 g/l) had unadjusted systolic pressures which were, on average, 2.9 mm Hg (95% CI -0.4 to 6.3) higher than those of other children (table 3). The adjusted systolic pressures were also highest in children of anaemic mothers. The children of mothers with mean corpuscular volumes of 80 fl or less (n=33) had systolic pressures which were, on average, 2.2 mm Hg (95% CI -1.3 to 5.7) higher than those of other children.

Birth weight fell from an average of 3377 g in mothers who did not smoke during pregnancy to 3178 g in mothers who smoked more than 20 cigarettes a day. However, the children's systolic

pressures were not associated with their mother's smoking history, parity, or age (table 3).

MOTHERS' AND FATHERS' BLOOD PRESSURES

The mean (SD) of the fathers' systolic pressure at the time of the study was 131.8 (14.0) mm Hg. Where both parents' blood pressures were recorded, we examined the separate relation of the child's pressure with its parents. The children's mean systolic pressure, adjusted for weight, rose by 1.2 mm Hg (95% CI 0.5 to 1.9) for every 10 mm Hg increase in mothers' systolic pressure, and by 0.7 mm Hg (95% CI 0.0 to 1.4) for every 10 mm Hg increase in fathers' systolic pressure. The corresponding figures for first born children were 1.8 (95% CI 0.6 to 2.9) and 1.9 (95% CI 0.7 to 3.1) and for later born children were 0.8 (95% CI -0.1 to 1.7) and 0.1 (95% CI -0.8 to 0.9).

SOCIAL CLASS

Children in social classes I and II had lower systolic pressures (table 4). Haemoglobin con-

Table 3 Mean children's systolic pressure (mm Hg) unadjusted and adjusted both for children's weight at 4 years and for mother's systolic pressure

	No	Unadjusted*	Adjusted*
Total	405	105.3	105.2
Mother's systolic pressure when child aged 4 years (mm Hg):			
≤110	99	103.3	
-120	128	104.9	
-130	96	105.1	
>130	82	108.7	
Mother's height (cm):			
≤159	103	105.9	106.0
-163	106	104.5	104.7
-167	99	104.9	104.9
>167	94	105.8	104.9
Lowest haemoglobin during pregnancy (g/l)			
<100	36	108.1	108.1
-109	88	105.8	105.9
-119	164	104.8	104.7
≥120	106	105.2	104.6
Cigarettes smoked/day during pregnancy:			
0	323	105.1	105.0
-10	34	106.2	105.9
-20	28	106.1	105.6
>20	19	105.2	106.1
Parity:			
First born	152	105.0	104.9
Later born	253	105.5	105.3
Mother's age at birth of child (years):			
≤25	92	105.2	104.9
-28	106	105.9	106.3
-31	92	105.2	104.8
>31	115	104.9	104.5

*SD of unadjusted values is 9.8 and of adjusted values is 9.4.

Table 4 Children's systolic pressure and mother's lowest haemoglobin concentration and mean corpuscular volume during pregnancy, by social class

Social class	No	Mean (unadjusted) children's pressure (mm Hg)	Lowest* haemoglobin (g/l)	Mean* corpuscular volume (fl)
I	34	103.6	115	86.8
II	100	104.7	114	86.8
III non-manual	43	105.4	111	87.0
III manual	121	106.0	113	85.3
IV and V	51	105.8	111	85.2
Total	349	105.3	113	86.1
(SD)		9.6	10	4.6

*Haematological indices were not known for 10 subjects.

centration during pregnancy was highest in social class I and II. Mean corpuscular volume was highest in mothers of social class I, II and III non-manual (table 4).

SIMULTANEOUS EFFECT OF FETAL SIZE AND MATERNAL INFLUENCES

Table 5 shows the simultaneous effects of child and fetal size and maternal variables on the children's systolic pressure. Weight at 4 years, placental weight, ponderal index at birth, mother's systolic pressure, and haemoglobin concentration during pregnancy all had independent relations with systolic pressure. We examined the relationship of mean diastolic pressure to the variables shown in table 5. The relations were similar to those with systolic pressure but the mean differences were smaller and none reached significance.

When systolic pressure was regressed on the same variables expressed continuously, rather than in groups, the results were comparable (table 6).

Discussion

We have examined the relations of systolic pressure to maternal and fetal influences in a series of 4 year old children, born in a maternity

unit which provides all hospital obstetric care for one health district. The children were selected only by their continuing residence in the health district. Blood pressure was measured with an automated recorder in the child's home by a standardised procedure. Efforts were made to minimise stress and disturbance to the child before and during measurement, but there was still considerable within child variation in systolic pressure, including a pronounced order effect. The mean (SD) of the third reading, 102.7 mm Hg (11.6), was 5.4 mm Hg above the 50th centile in the British standards, which were measured with a sphygmomanometer.⁶ In keeping with other studies we have used the average of the readings in our analysis. Average systolic pressure was positively related to weight at 4 years; this is in agreement with other studies in Britain^{1 6 7} and North America.⁸

The opposing relations of systolic pressure to birth weight and placental weight demonstrated in 50 year old men and women in Preston² were present in 4 year old children, though weaker. Systolic pressure at age 4 was inversely related to birth weight. This was independent of gestation and implies an association with reduced fetal growth, which is consistent with findings in 10 year old children in a national British cohort.¹ However, birth weight is a summary measure of fetal growth, which includes head size, length, and fatness. Further examination showed that systolic pressure was related to failure of head growth in relation to length and to a low ponderal index. Analysis of the Preston data has shown the same associations in adults (unpublished). To our knowledge neither of these associations with children's blood pressure has been described before. Both were significant. The nature of intrauterine influences that cause reduced head circumference and weight in relation to length are unknown and require further study.

The highest systolic pressures were found in children who had been small babies with large placentas, although the magnitude of the relations between pressure and placental and fetal size were smaller than in adults, even allowing for the smaller variation in children's blood pressure. Furthermore these relations were at the margin of significance and require confirmation in other samples of children. The causes of high placental weight and discordance between placental and birth weight are mostly unknown. Smoking during pregnancy is associated with reduced placental weight, though with a relatively greater decrease in birth weight than placental weight, and thus discordance between the two.⁹ We found no relation between

Table 5 Simultaneous effects of weight at 4 years, size at birth,* and maternal influences on systolic pressure, expressed as mean difference (95% CI) from the baseline

	No	Systolic pressure (mm Hg)
Weight at 4 years (kg):		
≤16.5	103	0.0 (baseline)
17-5	85	-0.1 (-3.0 to 2.7)
18-5	60	0.0 (-3.2 to 3.1)
>18.5	95	2.6 (-0.2 to 5.4)
Placental weight (g):		
≤550	90	0.0 (baseline)
650	97	0.3 (-2.6 to 3.1)
750	77	1.2 (-1.9 to 4.3)
>750	79	2.3 (-0.8 to 5.3)
Ponderal index (kg/m ³):		
<23	79	0.0 (baseline)
25	86	-0.8 (-3.8 to 2.3)
27.5	94	-2.4 (-5.4 to 0.5)
>27.5	84	-3.9 (-7.0 to -0.9)
Mother's systolic pressure (mm Hg):		
<110	81	0.0 (baseline)
120	109	1.6 (-1.2 to 4.4)
130	81	0.9 (-2.2 to 3.9)
>130	72	5.0 (1.9 to 8.1)
Lowest haemoglobin (g/l):		
<100	30	2.8 (-3.4 to 1.7)
109	77	0.3 (-2.7 to 3.3)
119	141	-0.9 (-1.3 to 6.8)
≥120	95	0.0 (baseline)

*Birth weight, length, and placental weight are adjusted for gestational age.

Table 6 Simultaneous effects of weight at 4 years, size at birth,* and maternal influences, expressed as continuous variables, on systolic pressure

	Regression slope	95% CI	p Value
Weight at 4 years (kg)	0.65	0.17 to 1.13	<0.01
Placental weight (g)	0.003	-0.003 to 0.009	0.4
Ponderal index (kg/m ³)	-0.41	-0.74 to -0.09	<0.05
Mother's systolic pressure (mm Hg)	0.12	0.04 to 0.19	<0.002
Lowest haemoglobin (<100 g/l v ≥100 g/l)	-3.1	-6.7 to 0.5	0.09

*Birth weight, length, and placental weight are adjusted for gestational age.

maternal smoking and the children's blood pressure (table 3).

The children's blood pressure was more closely related to the mothers' than the fathers' systolic pressure. This has been found before and has been ascribed to X linked genes.^{10 11} Another possibility is that higher blood pressure in a mother reflects her own fetal experience, which in turn influences the intrauterine environment she provides for her children. Studies of the Dutch famine have shown that women whose mothers were malnourished during pregnancy themselves had babies with retarded intrauterine growth.¹² The relation between the child's and father's pressure was found only in first born children, which suggest that in the later born the genetic contribution of the father's pressure is overridden by other factors. Our data do not allow further resolution of this.

We found that a maternal haemoglobin concentration below 100 g/l was associated with higher systolic pressure in the child, though this was not significant (table 3). Although haemoglobin may fall in pregnancy as a result of haemodilution, there is evidence that a haemoglobin concentration below 100 g/l is usually associated with iron deficiency.¹³ The lower mean corpuscular volumes and haemoglobin concentration in the lower social classes in our study are consistent with this (table 4). Although Salisbury has a relatively high socioeconomic status, 31% of mothers had haemoglobin concentrations below 110 g/l, the WHO definition of anaemia in pregnancy.⁵

Anaemia is associated with increased placental size,¹⁴ but this did not appear to be the sole mechanism of its relation with increased blood pressure, which was still present when considered simultaneously with the effects of placental weight (table 5). The rise in a child's blood pressure that is associated with anaemia could be a response to reduced maternal oxygen carrying capacity or a consequence of nutritional deficiency causing both anaemia and raised blood pressure. Findings in a rural community in the Gambia, West Africa, support a link between maternal nutrition and children's blood pressure. Failure of mothers to gain weight during the last trimester was associated with increased blood pressure in the child at 8 to 10 years.¹⁵ Better maternal nutrition could explain the lower pressures recently found in 5 to 7 year

old children in Guildford, a British town with relatively high socioeconomic status.¹⁶

Patterns of placental weight, birth weight, head circumference, and length that are associated with high blood pressure in adults are also associated with higher blood pressure in 4 year old children. We are carrying out a further study in another part of Britain to confirm this. Identification of the intrauterine influences which lead to these patterns of fetal growth could lead to the primary prevention of hypertension.

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Deficiency of prostacyclin production in meningococcal shock

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Abstract

A deficiency of prostacyclin (PGI₂) production by the vascular endothelium might underline the severe vasoconstriction and intravascular thrombosis that characterise meningococcal shock. The effect on PGI₂ synthesis by human umbilical vein endothelial cells (HUVEC) in culture was examined in sera from children with meningococcal shock, healthy adults, and children with other febrile illnesses. In comparison with adult controls, PGI₂ synthesis was reduced when HUVEC were incubated with the sera from 10 of 13 patients with meningococcal shock. A similar defect was observed with only four of 20 sera from children with other febrile illnesses. The effect of sera from patients with meningococcal shock on HUVEC was reversible with normal serum, and seems to be due to the absence of a factor necessary for PGI₂ production rather than an inhibitor.

These findings suggest that a deficiency of PGI₂ may have a role in the pathogenesis of meningococcal shock and that exogenous PGI₂ may be of therapeutic benefit.

Despite early diagnosis and appropriate treatment the mortality from meningococcal infection has not decreased over the last 30 years. The case mortality overall is 10% and rises to an unacceptable 40% for those with septicaemia and shock.¹ Attempts to improve the prognosis have so far been hampered by a lack of understanding of the pathophysiology of the disorder.

Clinical observation suggests that there are three major processes involved in the pathogenesis of meningococcal shock. Firstly, an increase in vascular permeability allows albumin to leak from the circulation, resulting in profound hypovolaemia and oedema.² Secondly, intense vasoconstriction of some vascular beds and dilatation of others leads to impaired organ perfusion.³ Thirdly, intravascular thrombosis of both large and small vessels associated with platelet and clotting factor consumption intensifies tissue ischaemia.⁴ These three features suggest that in meningococcal sepsis there is disruption of the homeostatic function of the endothelium that normally maintains vascular permeability and thromboresistance.

Disseminated intravascular coagulation, with activation of clotting factors and deposition of fibrin within the microvasculature, has been considered to be an essential component of meningococcal disease. Several studies have

documented both thrombocytopenia and derangement of coagulation.^{4,5} However, the mechanism responsible for the thrombocytopenia and the role of the disordered endothelial-platelet interactions in the pathophysiology of meningococcal infection have not been well studied.

Prostacyclin (PGI₂) is a potent inhibitor of platelet aggregation and a powerful vasodilator.⁶ It is released from membrane bound arachidonic acid and is actively produced by the vascular endothelium. Together with other important endothelium derived platelet inhibitory factors, such as nitric oxide,⁷ PGI₂ has an important role in thromboresistance. PGI₂ production increases appreciably in response to hypoxia and stress,⁸ suggesting that under these circumstances it may be particularly important in preventing intravascular platelet activation and tissue ischaemia.

We postulated that a deficiency of PGI₂ synthesis by the endothelium might be involved in the intravascular thrombosis and vasoconstriction seen in meningococcal disease. We suggest that this defect may be due to the absence of a factor necessary for PGI₂ production or the presence of an inhibitor in the serum of patients with the disorder. We therefore investigated the effect of sera from patients with meningococcal shock on endothelial PGI₂ production, and have compared this with that seen from sera from children with other febrile illnesses.

Patients and methods

PATIENTS WITH MENINGOCOCCAL DISEASE

Twenty three children (mean age 4.6 years; range 0.3 to 12.7 years) with severe meningococcal disease, referred to the Hospital for Sick Children, Great Ormond Street over the last six years, were studied. The diagnosis was made clinically on the basis of a characteristic purpuric rash in all cases and was confirmed by culture and/or serum antigen test in 18 patients. The haemophilus rapid antigen test was negative in the remaining patients. Shock was detected in 18 patients, this was defined by at least two of the following: impaired peripheral perfusion, as signified by poor capillary return, oliguria (less than 1 ml/kg/hour) or hypotension (at least 2 SD below the mean for age). Serum was available, in the acute phase, from only 13 of the patients with meningococcal shock.

CONTROLS

(a) Healthy adults

Serum was collected from 12 hospital workers

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who did not have a history of significant disease. This department has previously compared normal childhood and adult sera in the bioassay employed in this study and has not found any difference between the groups. Adult sera were therefore used to standardise the assay because of the ethical and logistic difficulties involved in obtaining samples from normal children.

(b) Children with other febrile illnesses

Serum was obtained from 20 children admitted to this hospital. Seven had non-meningococcal meningitis or encephalitis, one septicaemia, two Kawasaki disease, four toxic shock syndrome, two polyarteritis, and four had mild febrile illnesses. Shock, as defined by the criteria above, was diagnosed in six of these patients: four with toxic shock syndrome, one with haemophilus meningitis, and one with bacteroides septicaemia.

COLLECTION OF SAMPLES

Blood was collected within 24 hours of admission and serum separated within three hours. The samples were either used immediately or stored at -70°C until required.

CELL CULTURE

Human umbilical vein endothelial cells (HUVEC) were isolated by established methods⁹ and cultured in Dulbecco's modified Eagle's medium containing 3.5 g/l sodium bicarbonate to which 1% L-glutamine, 20% heat inactivated fetal calf serum, and 1% penicillin and streptomycin were added. Cells in first passage were grown to confluence in 24 well, flat bottom plates (Flow; 2.0 cm² per well).

BIOASSAY FOR PGI₂ PRODUCTION BY HUVEC IN CULTURE

Previously described methods were adapted to detect PGI₂ in the supernatant of HUVEC in culture.¹⁰ All experiments were performed in duplicate. Twenty four well plates with confluent HUVEC were maintained at 37°C in a heating block. The wells were aspirated to near dryness and then incubated, in duplicate, with 500 µl of culture medium (without fetal calf serum) containing 20% patient or control serum. After 10 minutes, 100 µl of culture supernatant was aspirated and added to 100 µl of normal platelet rich plasma (platelet count 300 to 500 × 10⁹/l). The mixture was stirred for one minute, in a PAP-4 (BIO/Data) aggregometer, the platelets were then challenged with ADP (2–4 µmol/l), and aggregation recorded. The inhibition of platelet aggregation by the culture supernatants was expressed as a percentage of the maximal aggregation obtained with platelet rich plasma and fresh medium that had not been incubated with HUVEC (percentage full aggregation). Neither patient nor control serum was found to affect platelet aggregation without prior incubation with HUVEC, excluding the possibility that the sera used contained a factor or factors that stimulate platelet aggregation.

Where supernatants were found not to inhibit

platelet aggregation, crossover experiments were performed. The culture supernatants used for the initial assay were removed and the cells were reincubated with fresh medium containing 20% control serum for 10 minutes. The culture supernatants were then assayed for recovery of PGI₂ activity.

MEASUREMENT OF 6-KETO PGF_{1α}

In order to confirm the results of the bioassay, the stable metabolite 6-keto PGF_{1α} was measured using a radioimmunoassay kit (Amersham). 6-Keto PGF_{1α} was measured in culture supernatants after incubation of HUVEC with the sera from seven children with meningococcal shock, which had been found not to induce PGI₂ production employing the bioassay method and eight normal adult controls.

STATISTICS

For the PGI₂ bioassay, a median and the 95% confidence intervals were calculated. The difference between the three patient groups was assessed using a Kruskal-Wallis analysis of variance. A rank sum test was employed to show the recovery of PGI₂ production by HUVEC and to express the results from the 6-keto PGF_{1α} assay.

Results

PGI₂ SYNTHESIS BY HUVEC

The sera from 12 normal adults induced PGI₂ synthesis by HUVEC (fig 1), as measured by inhibition of platelet aggregation by culture supernatants (median percentage full aggregation 21.5; 95% confidence interval 7 to 36). In contrast, the serum from 10 of 13 patients with meningococcal shock failed to support endothelial PGI₂ production (median percentage full aggregation 89; 95% confidence interval 36 to 98). Similar PGI₂ stimulating activity to the controls was observed with the sera from 16 of

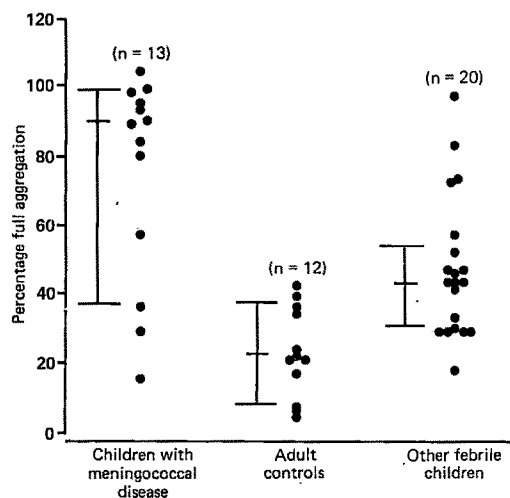


Figure 1 Human umbilical vein endothelial cell PGI₂ production after incubation with sera from patients with meningococcal shock, adult controls, and children with other febrile illnesses (Kruskal-Wallis analysis of variance, $p < 0.05$).

20 children with other febrile illnesses (median percentage full aggregation 43; 95% confidence interval 30 to 52). In four children, three with severe illness (pneumococcal meningitis, toxic shock syndrome, and bacteroides septicaemia respectively) and one with Lyme disease, PGI₂ production was diminished. The three patient groups were shown to be different by Kruskal-Wallis analysis of variance ($p < 0.05$).

The difference between the sera from the patients with meningococcal shock and the adult controls demonstrated by bioassay was confirmed using the 6-keto PGF_{1 α} radioimmunoassay. On incubation of HUVEC with sera from meningococcal shock patients, the median 6-keto PGF_{1 α} detected was 4.2 ng/ml (range 2.7–6.6) in comparison to 11.3 ng/ml (range 2.2–31) with HUVEC incubated with control sera (rank sum test, $p < 0.03$).

CROSSOVER EXPERIMENTS

When HUVEC previously cultured with sera from patients with meningococcal shock were reincubated with normal serum there was a significant increase in PGI₂ production (rank sum test, $p < 0.03$) (fig 2).

CHARACTERISATION OF THE DEFECT

Heating sera from patients with meningococcal shock to 56°C for either 10 or 30 minutes did not affect its activity. Storage of these sera for more than two weeks at 4°C did not change their effect on PGI₂ synthesis. Mixing experiments, employing the bioassay, have shown that addition of as little as one part normal serum to three parts serum from patients with meningococcal shock, restores the ability to induce endothelial PGI₂ production (results not shown), suggesting that normal serum is augmenting the meningococcal serum rather than reversing an inhibitor.

PLATELET AND CLOTTING STUDIES

Platelet and clotting studies were available from

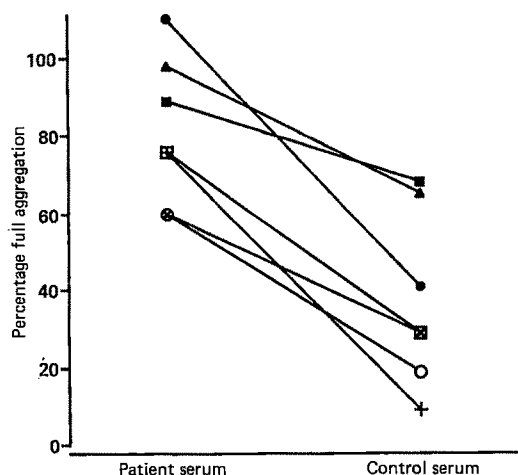


Figure 2 Crossover experiments. Human umbilical vein endothelial cells initially cultured with the sera from meningococcal patients and then reincubated with adult control sera recovered the ability to produce PGI₂ (rank sum test, $p < 0.03$).

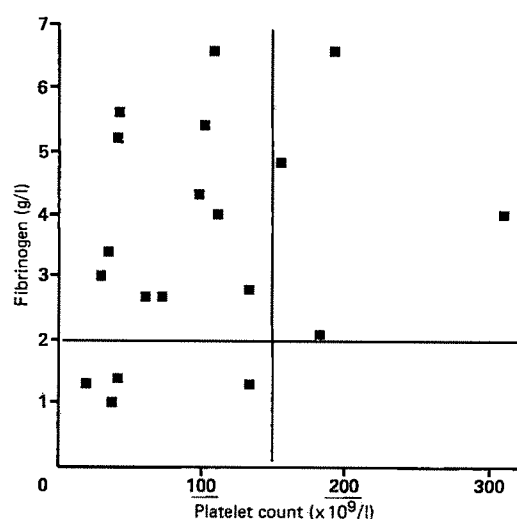


Figure 3 The platelet counts plotted against the fibrinogen concentrations from 19 children with severe meningococcal disease measured in the first 24 hours of the disease (bars indicate the lower limits of normal).

the records of 19 of the 23 children with severe meningococcal disease. In the first 24 hours after admission, 79% of these patients were thrombocytopenic but only 21% had low fibrinogen concentrations (fig 3). Platelet aggregation studies were performed on two patients with meningococcal shock. A poor response to ADP and adrenalin was observed, implying that in vivo platelet activation had occurred.

Discussion

We have shown a reduction in PGI₂ synthesis by HUVEC when incubated with the sera from 10 of 13 children with meningococcal shock when compared with normal controls. The abnormality was demonstrated both by the standard bioassay for PGI₂ and by the measurement of 6-keto PGF_{1 α} . The effect of sera from children with meningococcal shock on HUVEC was shown to be reversible, establishing that the PGI₂ deficiency was not due to a permanent alteration in endothelial cell function. The defect was not affected by heating to 56°C or by prolonged storage in the cold. Mixing experiments suggest that this phenomenon may be due to the absence of a factor necessary for PGI₂ synthesis rather than an inhibitor. The defect is not specific for meningococcal shock as it was also observed with the sera from four of 20 children with other febrile illnesses. The clinical manifestations and pathophysiology of severe infections overlap and it is therefore not surprising that similar defects may occur in the late stages of a variety of infections. None the less, if these in vitro findings reflect the in vivo situation, patients with meningococcal shock may have a defect in PGI₂ production by the vascular endothelium. This may be an important factor in the vasoconstriction, intravascular thrombosis, and platelet consumption seen in the disorder.

Impaired PGI₂ synthesis has been implicated in the pathogenesis of a number of other diseases, including sporadic haemolytic uraemic

syndrome,¹¹ systemic lupus erythematosus,⁶ and pre-eclamptic toxæmia.⁶ These conditions are all associated with endothelial damage, platelet activation, and the formation of microthrombi. We therefore looked for features of platelet activation and disseminated intravascular coagulation in 19 children with severe meningococcal sepsis in the first 24 hours of the illness. Whereas fibrinogen concentrations were normal or increased, thrombocytopenia was present in the majority of patients and was often profound and persistent. The impaired response to platelet agonists documented in the small number of patients studied by ourselves and others⁵ suggest that in meningococcal disease platelets circulate in an 'exhausted' form.¹² Animal studies have also demonstrated intravascular platelet activation in endotoxaemia,¹³ which together with the observed failure of heparin treatment to reduce the intravascular thrombosis of meningococcaemia,⁵ adds weight to the possibility that platelet activation and consumption may be more important than the depletion of coagulation factors in this disease.

If endothelial PGI₂ synthesis is diminished in meningococcal disease, this may be an important area for therapeutic intervention. In animal models, PGI₂ infusions have been shown to be effective in reversing the consequences of endotoxaemia, improving renal perfusion, and ameliorating intravascular thrombosis.^{13 14} Bihari and Tinker have found PGI₂ to be a valuable vasodilator in critically ill adults, improving oxygen delivery and so tissue oxygen consumption. Further studies to confirm the presence of defective PGI₂ production in vivo and to evaluate the potential use of exogenous PGI₂ in meningococcal shock are needed.

We would like to thank Ms J Cookson for her help and advice in the platelet work, Ms A Wade for her statistical advice, and Dr M Michaels for helping to collect the patient data. We would also like to thank Dr DJ Bihari and Dr I Murdock for their support. RSH is a Medical Research Council training fellow.

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Hyperganglionosis mimicking Hirschsprung's disease

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Abstract

Three patients with hyperganglionosis are reported in whom an initial diagnosis of Hirschsprung's disease was suspected. In one patient there was a classic presentation with constipation, in another Hirschsprung's disease coexisted, and in the third the initial inadequate suction rectal biopsy specimen was suggestive of Hirschsprung's disease on acetylcholinesterase staining. Evidence of hypertrophy and hyperplasia of the intermuscular and submucosal plexuses on a full thickness bowel biopsy specimen was used to confirm the diagnosis of hyperganglionosis, suggested by the characteristic demonstration of moderate increase in the number of acetylcholinesterase stained nerve fibres in the lamina propria mucosae on rectal biopsy. Surgical management was guided by clinical signs. Two patients had colonic resections; the third had temporary stomal diversion.

Hyperganglionosis is rarer than Hirschsprung's disease but is known to mimic it. We suggest full thickness bowel specimens are needed to confirm the diagnosis and that inadequate rectal suction biopsies must be interpreted with caution.

In 1970 a description of 'les megacolons avec hyperplasie des plexus myenteriques' was given by Nezelof *et al.*¹ They reported three paediatric patients with severe constipation in whom there was remarkable hypertrophy and hyperplasia of the submucosal and intermuscular ganglion plexuses on histology of rectal biopsy specimens. Two of the children had no extra-intestinal abnormality but the third developed a medullary carcinoma of the thyroid. From a review of the literature they noted that similar histological changes in the bowel had been reported, affecting the bowel alone, or in association with various endocrine tumours. There have been other more recent French case reports.²⁻⁴

In 1971 Meier-Ruge presented three further patients with a similar clinical condition.⁵ He stained rectal biopsy specimens for acetylcholinesterase and found there was increased activity of the parasympathetic nerve fibres in the lamina propria mucosae. There was also the occasional presence of isolated ganglion cells or smooth muscle in the lamina propria mucosae, in addition to hyperplasia and hypertrophy of the submucosal and intermuscular ganglion plexuses. He named the condition 'neuronal colonic dysplasia', which was taken up in other case reports.⁶⁻¹⁰

Subsequent authors working in collaboration with Meier-Ruge in Switzerland, Germany, and Chile,¹¹⁻¹³ and Munakata *et al* in Japan^{14 15} have called the condition 'neuronal intestinal dysplasia' and have reported larger series of cases occurring both alone and in association with Hirschsprung's disease. Garrett *et al* considered 'hyperganglionosis' a more accurate name for the condition as 'dysplasia' embraces all abnormalities of innervation of the bowel including Hirschsprung's disease.^{16 17}

Patients and methods

Between January 1984 and December 1987, 84 children were investigated for constipation or bowel obstruction with rectal biopsy (52 suction and 32 full thickness). Seventy one of these 84 biopsy specimens (84.5%) were stained for acetylcholinesterase by the method of Lake *et al.*¹⁸ The other 13 specimens (15.5%) were fixed, embedded in paraffin, and stained with haematoxylin and eosin.

The features looked for to make a diagnosis of hyperganglionosis were those of Meier-Ruge.^{11 19} (1) Hyperplasia of the submucosal and intermuscular plexuses with formation of giant ganglia. (2) Moderate rise in acetylcholinesterase activity in parasympathetic nerve fibres of the lamina propria mucosae and circular muscle, acetylcholinesterase activity being not as greatly raised as in Hirschsprung's disease. (3) The presence, sometimes, of isolated ganglion cells in the lamina propria mucosae and between the muscle layers of the muscularis mucosae. In addition we looked for the presence of thick nerve fibres in the submucosa, muscularis propria, and serosa.^{1 17}

We did not have the facilities to stain for adrenergic innervation and therefore could not look for the other feature mentioned by Meier-Ruge: hypoplasia or aplasia of the sympathetic innervation of the myenteric plexus. This feature however has not been confirmed by Garrett and Howard.¹⁶

Results

There were three patients with hyperganglionosis that was proved on a full thickness biopsy specimen, one of whom had coexisting Hirschsprung's disease. There were a further 14 patients with Hirschsprung's disease.

CASE HISTORIES

Patient 1

This patient was a twin whose mother was

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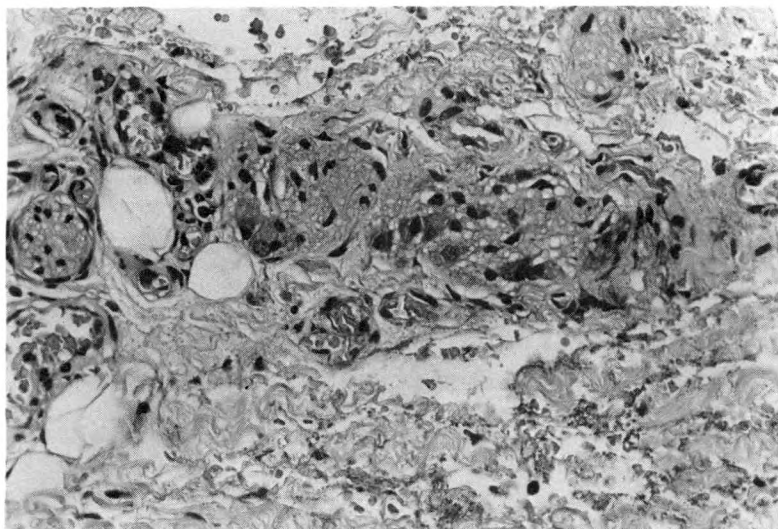


Figure 1 Patient 1. Large bowel wall submucosa showing increased numbers of thick tortuous nerve trunks and hyperplasia of ganglion cells. (Haematoxylin-eosin stain $\times 350$.)

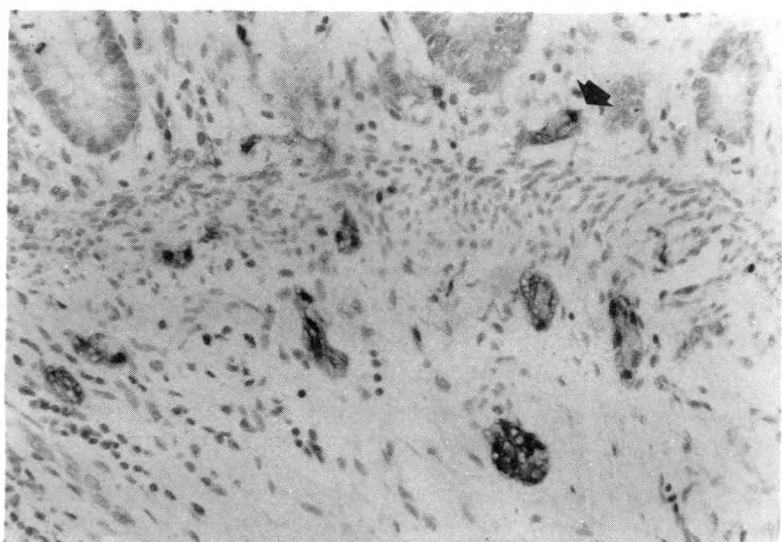


Figure 2 Patient 2. Large bowel wall. The submucosa contains numerous clusters of ganglion cells, some of which are very large. The occasional ganglion cell is seen in the lamina propria (arrow). (S-100 protein by immunoperoxidase method $\times 175$.)

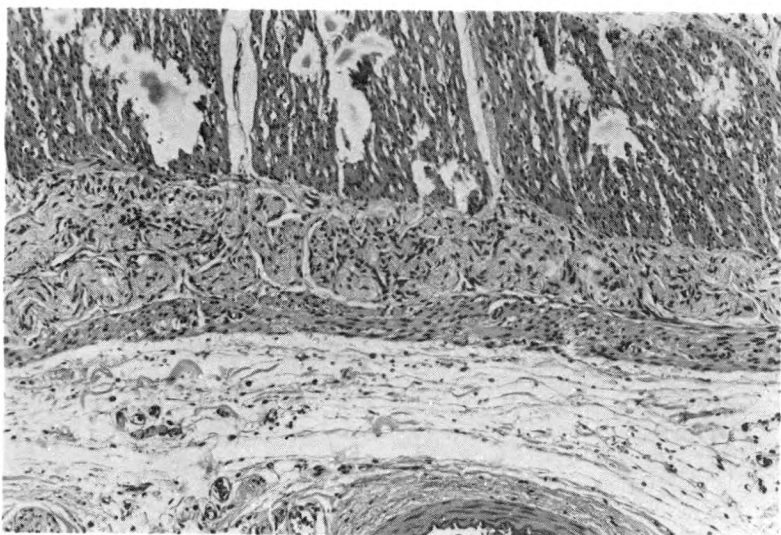


Figure 3 Patient 2. Large bowel wall showing hyperplasia of the nerve fibres in the intermuscular plexus. (Haematoxylin-eosin stain $\times 175$.)

diabetic. He presented on the third day of life with bile stained vomiting, abdominal distension, and delay in passing meconium. A plain radiograph of the abdomen showed bowel obstruction confirmed at laparotomy. A congested segment of ileum containing a milk plug was resected and a split ileostomy fashioned. Hirschsprung's disease was queried on the suction rectal biopsy specimen at 13 days but a repeat specimen one month later was suggestive of hyperganglionosis due to the prominent clumps of ganglion cells. At 4.5 months the ileum was reanastomosed and a sigmoid colostomy fashioned. The histology of the appendix revealed a striking appearance of a hyperplastic intermuscular plexus with many immature ganglion cells and thick nerve fibres breaking up the circular muscle. After a further four months the sigmoid colostomy was closed. The histology of the colon was similar (fig 1). The patient has continued to thrive and he has a normal bowel habit. His twin developed normally.

Patient 2

Aged 5.5 months this patient presented with severe constipation, a distended abdomen, and failure to thrive. The histology of a full thickness rectal biopsy specimen was suggestive of hyperganglionosis. A barium enema showed massive faecal loading of the colon. The diagnosis of hyperganglionosis was confirmed on repeat full thickness rectal biopsy. At 8 months of age a right transverse colostomy was carried out with removal of the appendix and Meckel's diverticulum, and full thickness biopsies of the transverse and sigmoid colon were taken. All showed hypertrophy and hyperplasia of the submucosal (fig 2) and intermuscular plexuses (fig 3). A barium distal loopogram revealed irregularity of the rectum and descending colon with residual barium at 24 hours. A total colectomy and ileorectal anastomosis was performed at 14 months. Histochemistry of the descending colon showed hyperganglionosis whereas the ascending colon was spared. He has gained weight satisfactorily and has regular bowel actions two or three times a day.

Patient 3

This 3 year old child presented with chronic constipation and abdominal distension. Hirschsprung's disease was diagnosed on a rectal biopsy specimen, which included mucosa, muscularis mucosae, and submucosa in which no ganglion cells were detected. A transverse colostomy was performed. During the Duhamel pull-through operation three months later a descending colon full thickness biopsy specimen was reported to be ganglionic on frozen section. The colon at this level was therefore anastomosed to the anorectal junction. Histology of the 16 cm of resected rectosigmoid was reported as showing ganglion cells in the proximal and middle levels with a 3 cm long aganglionic distal segment.

Large bowel obstruction developed after closure of the transverse colostomy, requiring

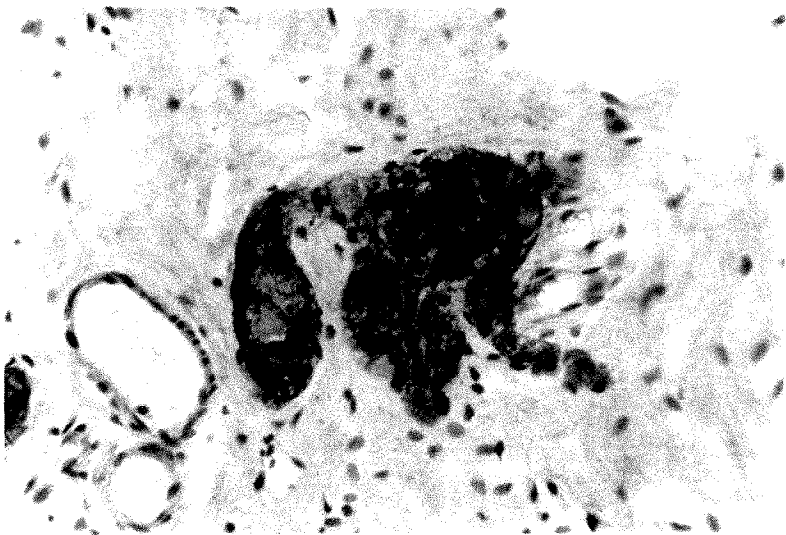


Figure 4 Patient 3. Large bowel wall. An example of a cluster of large, sometimes gigantic, ganglion cells. (S-100 protein by immunoperoxidase method $\times 350$.)

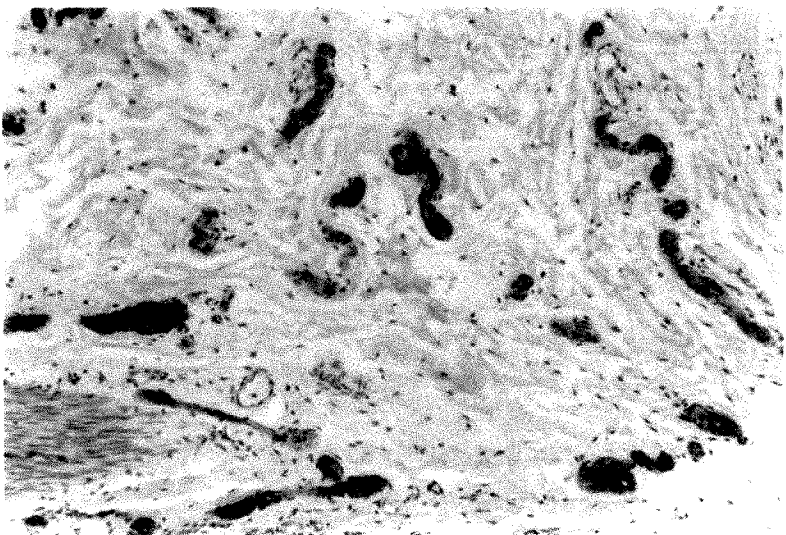


Figure 5 Patient 3. Large bowel wall showing increased numbers of thick and tortuous nerve trunks. (S-100 protein by immunoperoxidase method $\times 175$.)

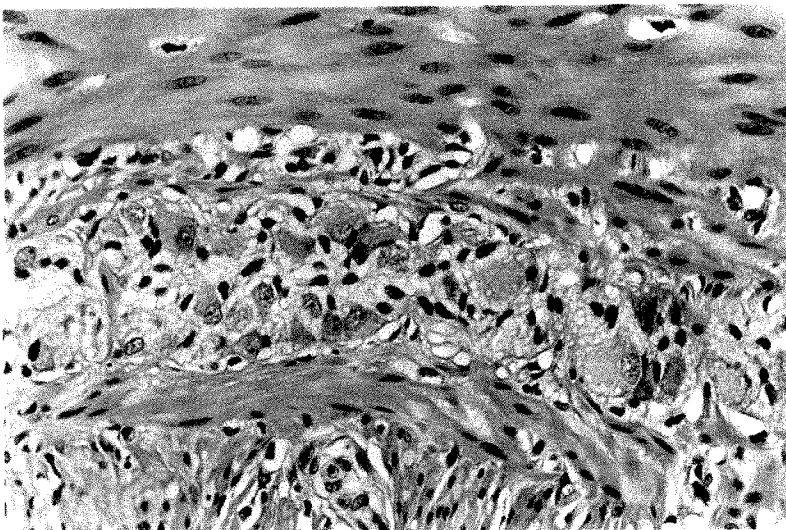


Figure 6 Patient 3. Large bowel wall showing hyperplasia and hypertrophy of the intermuscular plexus. (Haematoxylin-eosin stain $\times 350$.)

its reconstruction. Biopsy of specimens from left and right transverse colon showed an increased number and size of ganglion cells in both plexuses and the presence of thick cholinergic nerve trunks in the submucosa suggesting a diagnosis of hyperganglionosis. On review of the original specimen of excised rectosigmoid by the pathologist, very sparse ganglion cells were found in the section of its distal portion. The Duhamel operation was revised six months later, anastomosing ascending colon to the rectal stump, with a covering ileostomy. The entire resected colon showed the same histological changes as in the transverse colon, including the resection margins (figs 4-6). After closing the ileostomy the child remains well and has three bowel actions a day.

Discussion

Patients presenting with chronic constipation or with bowel obstruction in the neonatal period are frequently investigated to exclude Hirschsprung's disease, but hyperganglionosis may mimic this presentation.

Because of the similarity of appearance of the staining of the nerve fibre network in the lamina propria mucosae on acetylcholinesterase staining in Hirschsprung's disease and hyperganglionosis, it is essential to ensure that the suction rectal biopsy specimen contains adequate submucosa to confirm or exclude the presence of ganglion cells. In our first patient an erroneous initial diagnosis of Hirschsprung's disease was made because of the appearances of the lamina propria mucosae on an inadequate specimen. Meier-Ruge warned of this pitfall.¹⁹ The nerve network in hyperganglionosis is more prominent than normal but less prominent than that found in Hirschsprung's disease.

In two out of 10 of the cases reported by Munakata *et al* over 10 years the diagnosis of hyperganglionosis was made on acetylcholinesterase staining of a suction rectal biopsy specimen alone.¹⁴ We prefer to make the diagnosis when some other features that were mentioned by Nezeloff *et al* and Meier-Ruge are present on full thickness bowel specimens: hypertrophy and hyperplasia of the intermuscular as well as the submucosal plexus. In these three patients it took a period of one to four months and review of full thickness specimens before the condition was diagnosed with certainty. We suspected the condition in a further term baby unable to open her bowels without rectal washouts for the first four months of life in whom suction rectal biopsy appearances were suggestive of hyperganglionosis. However she recovered on conservative management and as there was no clinical indication for a full thickness rectal biopsy we were unable to confirm the diagnosis.

It could be argued that the diagnostic criteria for hyperganglionosis are subjective and 'observer dependent' so that, ideally, ganglion cell counts should be performed.^{10 20} However, having carried out a count of maximal number of ganglia per high power field in the rectal biopsy specimens of nine normal constipated children and our three patients (rectal biopsies

in the first two and a colonic biopsy in the third), there was too much overlap in the counts between the two groups to be useful. The histochemical and histological features of the condition are not all present on every specimen but we are persuaded that we noted sufficient of the features mentioned in the methods to confirm the diagnosis.

A hyperganglionic region of bowel existing proximal to an aganglionic segment in Hirschsprung's disease has been reported from several centres.^{8-12 14 15 21} These children may often present in the same way as our third patient, with bowel obstruction after the pull-through procedure.

There is a big discrepancy in the literature in the reported incidence of hyperganglionosis. Colleagues of Meier-Ruge have suggested it may be as common as Hirschsprung's disease¹² or 20% that of Hirschsprung's disease.¹³ Garrett and Howard¹⁶ and Risdon and Malone²² propose its comparative incidence is less than 5% that of Hirschsprung's disease. This suggests different diagnostic criteria are being used.

Some authors report poor peristalsis in hyperganglionic bowel but with functional improvement over months or years.^{12 14 15 23} This is illustrated by patient 1 who presented with small bowel obstruction managed with an ileostomy. This was subsequently closed and the patient thrived with a temporary sigmoid colostomy, and when this was closed had normal bowel function despite persisting histochemical change. In the second patient, who presented with gross constipation, it was decided to perform total colectomy because the barium loopogram demonstrated an irregular calibre of the colon with slow transit. In the third patient, who thrived with a right transverse colostomy, despite gross changes in the appendix, a repeat Duhamel pull-through was performed with the right colon. The surgical management is therefore not the same as in Hirschsprung's disease, where the length of the aganglionic segment precisely dictates the extent of bowel resected.

In conclusion, hyperganglionosis can mimic Hirschsprung's disease in its presentation. Acetylcholinesterase staining of suction rectal biopsy specimens is helpful in alerting the pathologist to the abnormality, but for differentiating it from Hirschsprung's disease adequate submucosa must be present. It is necessary to examine histologically more than one full thickness specimen of rectum or intestine to make a secure diagnosis of hyperganglionosis. The surgical management of the patients is based on clinical and radiological

criteria, and staged treatment with temporary stomas is recommended.

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Trends in prevalence and survival of very low birthweight infants, England and Wales: 1983-7

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Abstract

Between 1983 and 1987 over 99% of all infants born in England and Wales had their birth weights recorded when the birth was registered. Trends in occurrence and one year survival of those who weighed under 1500 g at birth have been calculated in 100 g groups, separately for single and multiple births. By 1987 singleton live births in England and Wales who weighed between 700 and 799 g had a 43% chance of surviving to 1 year compared with a 32% chance five years earlier; those who weighed 800 to 899 g had a 55% chance compared with 46%. The absolute number of survivors weighing between 500 and 999 g at birth increased by nearly 50% between 1983 and 1987, and there was a 30% increase overall in survivors weighing less than 1500 g.

Infants of very low birth weight (less than 1500 g) are of considerable importance because of the large contribution they make to early deaths, the resources required for their care in the neonatal period, and most of all because of their increased risk of long term disability.^{1 2} Their risk of death and morbidity is closely related to their weight, the risks rising sharply as birth weight falls.

Between 1983 and 1987 over 99% of all infants born in England and Wales had their birth weight recorded when the birth was registered, so that it is now possible for us to describe trends in occurrence and one year survival in 100 g groups separately for single and multiple births.

To help in the planning of their care, and the evaluation of the effects of medical intervention on their survival, the present study gives information on the frequency of births under 1500 g and their mortality.

Methods

BACKGROUND TO INFORMATION AVAILABLE

The birth weight for infants weighing 5.5 pounds (2494 g) or less (but not more) has been collected in England and Wales since 1952, but has been available only in aggregated weight categories.³ Since 1975, however, provision has been made for birth weight to be entered on to the drafts of all birth certificates for live infants. The birth weight is copied from birth notifications sent from health authorities to the local Registrar of Births, Marriages and Deaths and now complements information given by the parents when the birth is registered. For some

years after 1975 birth weight was not completed, particularly for infants who died early, but between 1983 and 1987 it was obtained for over 99% of all live births.⁴

Data on occurrence and mortality by birth weight has been published regularly in publications from the Office of Population Censuses and Surveys (OPCS) annually but the breakdown has never been finer than 500 g groups.⁵ This paper is confined to infants weighing less than 1500 g at birth; results are presented in 100 g groups and for single and multiple births separately. This grouping was prepared for the second full meeting of the International Collaborative Effort on Perinatal and Infant Mortality (ICE).⁶

There are a number of problems in the interpretation of the data. In England and Wales gestational age is obtained for stillbirths but not for live births, and babies that are born dead cannot be registered as stillbirths unless the pregnancy reached 28 completed weeks of gestation. All live births can theoretically be registered regardless of birth weight or gestational age, but—particularly with very preterm birth—there can be differences in opinion about what is considered to be a miscarriage rather than a live birth, or a stillbirth rather than a live birth. The attitudes of professionals towards the age of viability may affect the maturity threshold at which resuscitation is offered,⁷ and there are international differences in the perceptions and regulations governing definitions of viability.^{8 9}

CALCULATION OF RATES

We have calculated mortality rates for deaths under the age of 1 year in children born in a given calendar year (birth cohort), even if the death occurred in the year after the birth. This was made possible by linking information from registrations of births and of infant deaths. The more conventional method of analysis is to relate the number of deaths in a given period (death cohort) to the births during the same period, even if the death was of a child born before the beginning of the period. Discrepancies between the use of birth and death cohorts are normally small and relate particularly to postneonatal deaths. Both are available from OPCS annual reports but the mortality rates for birth cohorts are not available until a year after those based on death cohorts.⁵

Results

TRENDS IN NUMBERS REGISTERED

Table 1 shows the numbers of infants born

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Table 1 Number (%) of live births weighing <1500 g. England and Wales 1983-7

Birth weight (g)	1983	1984	1985	1986	1987
<400	64 (0.01)	65 (0.01)	73 (0.01)	82 (0.01)	67 (0.01)
400-	57 (0.01)	78 (0.01)	68 (0.01)	66 (0.01)	83 (0.01)
500-	154 (0.02)	152 (0.02)	147 (0.02)	178 (0.03)	198 (0.03)
600-	234 (0.04)	253 (0.04)	304 (0.05)	336 (0.05)	324 (0.05)
700-	309 (0.05)	332 (0.05)	361 (0.05)	400 (0.06)	412 (0.06)
800-	405 (0.06)	463 (0.07)	409 (0.06)	477 (0.07)	503 (0.07)
900-	493 (0.08)	531 (0.08)	560 (0.09)	526 (0.08)	556 (0.08)
1000-	565 (0.09)	610 (0.10)	625 (0.10)	654 (0.10)	758 (0.11)
1100-	616 (0.10)	635 (0.10)	690 (0.11)	680 (0.10)	754 (0.11)
1200-	689 (0.11)	671 (0.11)	706 (0.11)	813 (0.12)	816 (0.12)
1300-	824 (0.13)	817 (0.13)	926 (0.14)	822 (0.12)	958 (0.14)
1400-	896 (0.14)	947 (0.15)	1031 (0.16)	1047 (0.16)	1076 (0.16)
All <1500	5306 (0.84)	5554 (0.87)	5900 (0.91)	6081 (0.91)	6505 (0.95)
Not known	865 (0.14)	812 (0.13)	868 (0.13)	624 (0.09)	502 (0.07)
All live births	629134 (100)	636818 (100)	656417 (100)	661018 (100)	681511 (100)

weighing less than 1500 g and the percentage they formed of all births from 1983-7. There was a rise of 23% in the absolute numbers of registered live births of these weights, partly because there was an increase of 8% in births of all weights and partly because the proportion of all live births who had a birth weight of less than 1500 g rose from 0.84% in 1983 to 0.95% in 1987.

Table 2 gives the numbers by live births and stillbirths, and by single and multiple births. There was an increase of 21% in the number of live born singletons weighing less than 1500 g between 1983 and 1987, and an increase of 28% in multiple births. With the exception of the very lowest weight groups, the numbers of stillbirths actually fell over the period. Nevertheless, taking live births and stillbirths together, the total number of infants born weighing less

than 1500 g still increased over the period, by 16% for singleton and 24% for multiple births. Multiple births account for about one fifth of these very low birthweight babies.

INFANTS OF UNKNOWN BIRTH WEIGHT OR REPORTED TO HAVE WEIGHED LESS THAN 500 G
Table 3 gives the birthweight specific infant mortality rates for birth of less than 1500 g, and for births of unknown weight, separately for the years 1983 to 1987. In each year the mortality rates of those weighing less than 500 g are lower than those of babies weighing between 500 and 799 g. Moreover, babies of unknown weight have high infant mortality rates. For singletons these approximate to those of babies who weighed between 1200 and 1299 g in 1983, and to those who weighed between 1000 and 1099 g

Table 2 (A) Birth weight distribution in 1983 and 1987 for single and multiple births, and live births and stillbirths

Birth weight (g)	1983				1987			
	Live births		Stillbirths		Live births		Stillbirths	
	Single	Multiple	Single	Multiple	Single	Multiple	Single	Multiple
<500	98	23	36	20	126	24	59	16
500-	117	37	26	6	138	60	38	6
600-	183	51	58	8	266	58	58	11
700-	261	48	88	12	335	77	80	11
800-	339	66	90	11	412	91	72	7
900-	403	90	106	11	427	129	97	6
1000-	464	101	133	11	633	125	111	6
1100-	515	101	121	10	625	129	95	11
1200-	576	113	105	20	633	183	100	19
1300-	653	171	116	9	758	200	96	18
1400-	677	219	104	13	848	228	97	13
All <1500	4286	1020	983	131	5201	1304	903	124
Not known	810	55	35	17	474	28	22	11

(B) Percentage change from 1983 to 1987 for single and multiple births, and live births and stillbirths

Birth weight (g)	Live births		Stillbirths		All single	All multiple
	Single	Multiple	Single	Multiple		
<500	29	4	64	-20	38	-7
500-	18	62	46	0	23	53
600-	45	14	0	38	34	17
700-	28	60	-9	-8	19	47
800-	22	38	-20	-36	13	27
900-	6	43	-8	-45	3	34
1000-	36	24	-17	-45	25	17
1100-	21	28	-21	10	13	26
1200-	10	62	-5	-5	8	52
1300-	16	17	-17	100	11	21
1400-	25	4	-7	0	21	4
All <1500	21	28	-8	-5	16	24
Not known	-41	-49	-37	-35	-46	-46

in 1987. For multiple births the mortality of those of unknown weight is consistently higher than the average for all those known to have weighed less than 1500 g.

Between 1983 and 1987 there was a decrease in the total number of infants of unknown birth weight from 917 to 535 (table 2). These almost certainly include some of low birth weight, as indicated by the high proportion of multiple births (6% of live births and 33% of stillbirths in 1987) and their high infant mortality rates. The proportion whose birth weight was unknown is highest among stillbirths, being 1.0% of all stillbirths in 1987 compared with 0.1% of live births, and among multiple births, 4% among stillbirths, 0.2% among live multiple births.

The increase in the proportion of very low birthweight babies born between 1983 and 1987 is not, however, just an artefact caused by a decrease in the proportion for whom the weight was unknown. Even if all those of unknown weight are included with those known to have weighed less than 1500 g there would still have been an increase of 10% in the proportion of very low birthweight babies born between 1983 and 1987 compared with 8% in all births.

There must also be some doubt about the accuracy of the birth weights of live born babies registered as weighing less than 500 g, whose mortality rates are lower than those of slightly heavier babies. The number of such births rose from 121 to 150 between 1983 and 1987, an increase of over 20%. Analysis of data gathered since 1987 suggests that the increase in the use of metric birth weights may be increasing the number of transcription errors, particularly those which result in babies of 3000 or 4000 g being recorded as weighing 300 or 400 g. It is likely that some of these extremely low weights have been misclassified in this way, and may be contributing towards the increase in numbers of those registered as of very low birth weight, although the numbers are too small to have a serious effect.

TRENDS IN INFANT MORTALITY RATES

The most important feature shown in table 3 is the continuing reduction in birthweight specific infant mortality among singletons over the period, although the annual patterns in the individual weight groups from 500 g upwards are slightly inconsistent. The changes are summa-

risied in fig 1 by averaging rates for the first three, and last two, years of the period. There is a fall in infant mortality in each 100 g weight group, the biggest falls being in those who weighed between 700 and 900 g. The pattern for multiple births is different (fig 2) and shows no consistent improvement.

Table 3 also shows that, for the lowest birth weights, multiple births have higher mortality rates than singletons. This pattern is reversed at higher weights, the turning point varying by year, but becoming pronounced and quite consistent at weights of 1300 g or more.

RATIO OF STILLBIRTHS: INFANT DEATHS

At the lower tail of the birth weight distribution the problem of definition of viability means that the ratio of stillbirths: infant deaths is affected, because live births but not fetal deaths can be registered under 28 weeks' gestational age. Table 4 shows that in each of the years concerned at birth weights of less than 1000 g,

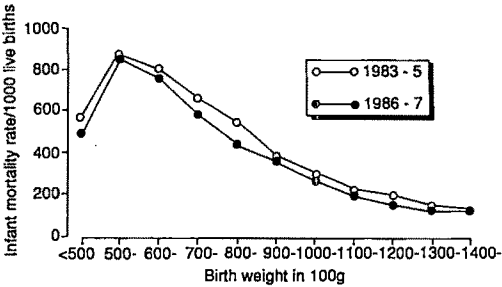


Figure 1 Averaged infant mortality rates for singleton births weighing <1500 g for 1983-5 and 1986-7.

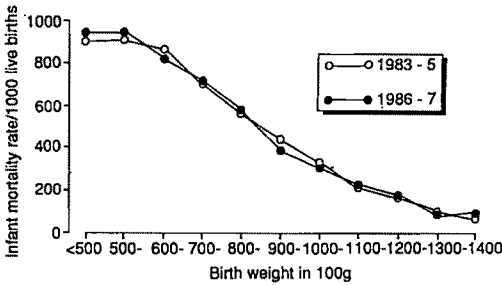


Figure 2 Averaged infant mortality rates for multiple births weighing <1500 g for 1983-5 and 1986-7.

Table 3 Trends in infant mortality rates/1000 live births of very low birthweight infants: England and Wales 1983-7

Birth weight (g)	1983		1984		1985		1986		1987	
	Singleton	Multiple	Singleton	Multiple	Singleton	Multiple	Singleton	Multiple	Singleton	Multiple
<500	592	783	565	964	530	961	458	933	532	958
500-	897	1000	849	939	866	800	899	959	804	933
600-	858	843	787	863	772	889	738	783	793	862
700-	678	771	666	680	643	672	598	710	567	727
800-	540	530	538	670	555	508	439	598	449	571
900-	427	500	366	412	347	405	397	369	323	403
1000-	349	366	285	286	249	308	247	321	289	288
1100-	239	218	216	259	223	161	188	220	206	225
1200-	226	186	168	229	189	86	162	144	155	202
1300-	167	82	142	108	123	109	125	81	128	80
1400-	123	82	128	28	136	81	135	114	111	61
All <1500	340	321	311	341	302	299	265	324	289	323
Not known	204	436	207	442	156	565	178	407	221	500
All weights	9.38	40.7	8.52	41.6	8.78	39.2	8.35	45.3	8.36	42.7

the ratio of stillbirths:infants deaths was smaller than among those weighing between 1000 and 1499 g.

AGE AT DEATH

Babies weighing less than 1500 g often die at very young ages, so that they contribute disproportionately to very early deaths. In 1987, 27% of all infant singleton deaths had weighed less than 1500 g at birth, but only 0.8% of singleton live births had been of this weight. Fifty four per cent of all singleton live born babies that died during the first 30 minutes had weighed less than 1500 g. Although this proportion fell with increasing age at death, there was an excess of babies of this weight even in the deaths occurring between 9 months and 1 year,

of which 6% had weighed less than 1500 g. The pattern for multiple births was similar but even more pronounced. Sixty eight per cent of all infant deaths of babies from multiple births in 1987 had been reported as weighing less than 1500 g at birth, and 92% of deaths among multiple births that occurred within 30 minutes of birth had been of this weight, compared with a third of deaths of multiple births between 9 months and 1 year of age.

Table 5 shows the proportions by age at death of all those weighing less than 1500 g at birth in 1983 and 1987. The proportion of all deaths that happened during the postneonatal period rose slightly from 11.8% in 1983 to 12.8% in 1987 in singletons, and from 11.6% to 12.3% in multiple births.

Table 4 Numbers of infant deaths and stillbirths weighing less than 1500 g—multiple plus singleton births: England and Wales 1983-7

Year	Birth weight (g)			
	Infant deaths		Stillbirths	
	<1000	1000-1499	<1000	1000-1499
1983	1067	719	472	642
1984	1109	650	490	612
1985	1112	668	499	580
1986	1173	663	479	621
1987	1191	733	461	566

TRENDS IN NUMBERS OF INFANTS SURVIVING

Between 1983 and 1987 the rise in the registered occurrences, together with the improvement in survival, led to an increased number of very low birthweight survivors at 1 year (table 6). Overall, the absolute number of singleton survivors reported as having a birth weight of less than 1500 g increased by 31% between 1983 and 1987, and that of multiple births by 27%. The number of survivors weighing between 500 and 999 g at birth increased even more, singletons by 46% and multiple births by 58%.

Table 5 Time of death by birth weight and multiplicity, England and Wales: 1983 and 1987

Infant deaths	1983				1987			
	Singleton		Multiple		Singleton		Multiple	
	No	%	No	%	No	%	No	%
All weights	5786	100	513	100	5573	100	620	100
All <1500 g	1459	25	327	64	1503	27	421	68
All <1500 g	1459	100	327	100	1503	100	421	100
<30 Minutes	94	6	16	5	114	8	36	9
-1 Day	622	43	142	43	604	40	145	34
1-6 Days	394	27	92	28	378	25	130	31
7-27 Days	176	12	39	12	215	14	58	14
All neonatal deaths	1286	88	289	88	1311	87	369	88
28 Days-2 months	91	6	18	6	85	6	22	5
3-5 Months	41	3	16	5	65	4	17	4
6-8 Months	31	2	2	1	32	2	8	2
9-11 Months	10	1	2	<1	10	1	5	1
All postneonatal deaths	173	12	38	12	192	13	52	12

Table 6 Birth cohort survivors at 1 year by birth weight, England and Wales: 1983-7

Birth weight (g)	No of survivors at 1 year*									
	1983		1984		1985		1986		1987	
	Singleton	Multiple	Singleton	Multiple	Singleton	Multiple	Singleton	Multiple	Singleton	Multiple
<500-	40	5	50	1	54	1	64	2	59	1
500-	12	0	18	2	15	7	13	2	27	4
600-	26	8	43	7	55	7	70	15	55	8
700-	84	11	94	16	106	21	133	20	145	21
800-	156	31	172	30	153	32	216	37	227	39
900-	231	45	275	57	293	66	255	65	289	77
1000-	302	64	361	75	401	63	394	89	450	89
1100-	392	79	410	83	440	104	449	99	496	100
1200-	446	92	460	91	469	117	541	143	535	146
1300-	544	157	582	124	651	163	569	158	661	184
1400-	594	201	667	117	720	182	693	218	754	214
All <1500	2827	693	3132	603	3357	763	3397	848	3698	883

*Calculated as number of live births minus infant deaths.

Discussion

The aim of this report was to make data available from a new national data set that show trends in the incidence and survival of infants weighing under 1500 g at birth. The main findings were an increase in the absolute number and the incidence of these births, and a fall in their infant mortality.

Some of the observed rise in the proportion of babies of very low birth weight from 0.84% in 1983 to 0.95% in 1987 may be the result of an increase in the proportion of triplets and higher order multiple births¹⁰; some is probably the result of a change in clinical perception, shifting the reported outcomes from non-registrable miscarriages to registered births; and some is the result of a decrease in the proportion for whom birth weight was not reported. Additionally, there is a suggestion that there may be a shift from stillbirths to live births, but in the absence of information about registration practices of very low weight stillbirths this will be difficult to prove. These issues were recently discussed in some detail at a meeting of the International Collaborative Effort into Perinatal and Infant Mortality.⁶ It was thought that for complete reporting there should be a legal limit of viability defined in weeks of gestation, set at a point some weeks earlier than the maturity at which registrations may be expected to be reliable.

The next point to be considered is the evidence about the validity of reported weights at the lowest birth weights. There have long been problems caused by the dual use of imperial and metric measures of birth weight, which lead to digit preference when half or quarter pounds are converted to grams. Moreover, as stated earlier, this may also be leading to errors in placing the decimal point, which results in weights of 3000 or 4000 g being reported as 300 or 400 g. Although the numbers may be small such mistakes may have considerable effects on national statistics in this weight range. These are errors that should be eliminated by careful quality checks and the availability of data about gestational ages. The number of babies of unknown weights, which is often biased by a excess of stillbirths or infant deaths, should also be considered in the interpretation of changes in mortality rates over time.

Overall, however, during the years considered, the quality of data seems good enough to confirm the increase in survival to 1 year for babies of these very low weights, particularly for singletons weighing between 700 and 900 g. By 1987 a singleton live birth weighing between 700 and 799 g had a 43% chance of surviving to 1 year compared with a 32% chance five years earlier; one weighing 800 to 899 g had a 55% chance compared with 46% in 1983. The lack of improvement in survival of multiple births is probably related to the sharp increase in the number of the particularly high risk triplets and higher order multiple births.¹⁰

The number of survivors, both single and multiple, who weighed between 500 and 999 g at birth increased by nearly 50% between 1983 and 1987. Such babies are of course also at high risk of morbidity, and the increased number underlines the need for ongoing surveillance of their outcome, and for the maintenance of high quality data about the circumstances of their birth and their maturity.

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What do parents expect antenatally and do babies teach them?

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Abstract

Antenatal inquiry of 658 parents in the North Staffordshire District Health Authority showed at least 13% to lack knowledge about a baby's potential for personal interaction when under 1 week old. Mothers and fathers varied significantly, independent of parity. Experienced parents expected later smiles. Two hundred and seventy eight of the same families were questioned three to four months after birth. Most parents had observed their baby's early responsiveness. Specific responses (looking, listening) were noted earlier when anticipated and looked for. Significant among postnatal non-responders was their antenatal selection of predominantly impersonal stimulation for a baby. The greatest degree of warmth noted in postnatal observations correlated notably with a father's antenatal interest and postnatal support from him and their friends, a mother's commitment to breast feeding and her knowledge that a very young baby can see, likes faces, and cries for emotional reasons. This highlights areas for antenatal tuition and postnatal encouragement, aiming to enhance warm early mutual regard between parents and child.

Research on normal full term babies over the past two decades indicates how soon they show responses along all sensory pathways.¹ Visually, the preferred pattern from day one is a face, particularly the eyes and brow. The optimal focal distance is that between an admiring face and the baby's when a child is held in the crook of the admirer's arm. Responsive interaction accelerates the baby's identification of key people.²⁻⁴ There can be a form of smiling from the first day with clearly responsive smiles by 2 to 4 weeks of age.⁵ Imitative behaviour has been noted by 3 days⁶ and recognition of the mother by smell within a week.⁷ Though some babies, like adults, express themselves more readily than others, the infant appears to be innately disposed to respond to human more than mechanical qualities and can be the one to initiate communication with a consistent care giver.⁸

Work on the father-infant relationship has until recently been neglected. A father's preliminary engrossment at the time of birth does not exclude the risk of paternal alienation later on unless his continued involvement is encouraged.⁹ Researchers now recognise all this, paediatricians are learning it with interest, but to what extent do parents recognise the competence of their own babies?

The aims of the study were to determine whether fathers and mothers have different expectations about a newborn baby's responsiveness, whether these are correct, whether previous experience of babies alters them, and whether (and what) a baby later teaches parents. This could affect both antenatal instruction and postnatal reinforcement. To enhance parent-baby interaction encourages the growth of warm parental understanding which then should forestall deprivation and abuse.

Subjects and methods

In 1987-8, 416 mothers and 242 of their partners separately answered structured questionnaires issued in two specified weekly antenatal clinics of the North Staffordshire Maternity Hospital, Stoke on Trent, the goal being to assess at least 200 primiparous and 200 multiparous women and their partners. The questionnaire was given to willing mothers of 18 years old or more whose partners (in person or via the mothers) were offered a questionnaire. Both documents were to be completed at once or posted back. There were 214 first time mothers, 125 first time fathers, 202 multiparous mothers, and 115 experienced fathers. The status of two fathers was unrecorded. Twenty one percent of the fathers came from socio-economic groups I/II, 49% from group III, and 18.5% from groups IV/V, 11.5% being unknown or unemployed.

Parents were identified by name and three to four months after the birth were sent a prepaid, postal, open ended questionnaire. Because of the poor response to the fathers' antenatal questionnaire and to encourage discussion about their baby this was a shared exercise. Altogether 278 of the original 416 families responded and their personal antenatal and postnatal results were compared and contrasted. Although not all parents answered each question, enough did so to make comparisons valid. Relevant numbers appear in the text.

The *P score* (0-3) was gauged postnatally and recorded the degree of paternal involvement indicated by a father's presence at the birth, by spontaneous reference to him in answer to two questions about the mother's preferred advisers and actual supporters, and two other questions about the baby's selective responsiveness to faces and voices. Any extra mention of the father gained a sixth mark, two marks then contributing one point for the final *P score*. The *RR score* (1-3), also postnatal, attempted to determine reciprocal regard between parents and baby and indicated the means by which

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firm two way attachment was growing. It was cumulatively scored, with points given for mention of the baby's personal as well as physical needs, the parents' recollection of the child's personally interactive behaviour, and the overall warmth of their answers. Original continuous data from 278 responsive families was categorised into the three grades, approximately equal numbers being allocated to each. (Independent evaluation by ED and JG agreed, small variations in raw scores leaving the final RR grade unaffected.)

STATISTICAL ANALYSIS

Yes/no answers were tabulated as percentages and subgroups compared by age, education, socioeconomic group, first or subsequent baby, and father/mother. Small subgroups of mothers were compared on the variables of parity, age, and education.

The tables give total numbers in each parent group, but to exclude bias by collusion antenatal fathers and mothers were compared by paired tests. The χ^2 test of association in categorical data and in some cases Fisher's exact test were used. The sign test was used to compare paired ordinal data. Standard normal values, corrected for continuity, were employed to test difference between proportions where the sample sizes were large. Tests between groups of continuous measurements were based on the percentage points of the standard normal, Student's *t*, and F distributions. Most of the analyses were carried out using the NCSS statistical package.¹⁰

Table 1 Maternal and paternal background and expectations by age

Category (% who would have:)	Age of mother (years)			Age of father (years)		
	<22 (n=94)	22-29 (n=225)	>29 (n=97)	<24 (n=46)	24-31 (n=130)	>31 (n=65)
First baby	70	50	35	71	51	38
Left school <17 years	90	41	70	43	101	44
Intended to breast feed	34	54	79	62	68	69
Asked information of parents	69	50	35	47	27	31
Asked information of professionals	24	38	38	5	12	10
Expected help from parents	65	47	41	42	38	30
Expected help from professionals	14	24	21	8	11	18
Expected help from peers	7	8	8	11	6	4
Expected help from partner	50	52	58	—	—	—
Attended antenatal classes	54	54	58	12	19	24
Learnt about child care at school	56	36	15	4	2	3
Learnt about child development	51	25	9	10	8	4
Post-school training in childcare	9	8	6	0	22	18
Held a baby	98	98	97	42	56	57
Changed a nappy	90	80	82	12	19	24
Read hospital literature	93	93	89	78	69	78

Table 2 Major areas of antenatal parental ignorance about a baby's abilities

Parent believes that:	No (%) mothers	No (%) fathers	p Value	No of paired data	χ^2 (1df)
At birth:					
Not at all responsive	223/381 (58.5)	159/211 (75.4)	<0.001	202	14.66
No response to talk	106/416 (25.5)	85/238 (35.7)	<0.001	238	15.73
No visual response to shapes	118/408 (28.9)	45/239 (18.8)	<0.001	235	12.70
No visual response to faces	136/410 (33.2)	103/239 (43.1)	<0.001	237	16.05
At one week:					
Not enjoying talk	56/416 (13.5)	49/238 (20.6)	NS		
Not enjoying shapes or faces	54/407 (13.3)	31/237 (13.1)	NS		
Up to 3 months:					
Not yet learning	64/415 (15.4)	48/238 (20.2)	NS		
At 3 months:					
Cries because naughty	54/414 (13.0)	30/241 (12.4)	NS		

Results

ANTENATAL INQUIRY

Past experience and general expectations (table 1)

Particularly when young or less well educated, more mothers than fathers had learned about child care or development at school. Attendance at antenatal classes was higher among mothers, though a little more likely among fathers from socioeconomic groups I/II (22%) than those in groups III (18%) or IV/V (17%). Women were more likely than men to expect help from professionals. Both, particularly when young, tended to ask information of their own parents. However, more fathers in socioeconomic groups I/II (25%) expected professional help than in groups III (8%) or IV/V (9%) with a reversal of this trend (24%, 33%, 40%) among those seeking advice from their own parents. More multiparous (67%) than primiparous (51%) women anticipated major help with the baby from their partners. Over half the parents studied said that television had given helpful information about babies. More fathers under 30 years wanted their baby to be breast fed than did mothers. Intent to breast feed was found more in better educated women than in early school leavers (73%, 51%) and in those from socioeconomic groups I/II more than III or IV/V (77%, 54%, 49%).

Differences between mothers and fathers for levels of antenatal ignorance and experience

Responsiveness—The word response conjured up different images but the mean (SD) maternal value of a baby's first response was 28.6 (45.5) days and that of fathers was 47.7 (66.5) days, paired difference in mean 24.0 days: $Z=4.93$, $p<0.001$ ($n=201$).

Most parents gave many appropriate answers about the timing of specific responses, by the end of the first week correctly expecting their baby to be learning (over 50%), listening to voices (over 80%), and reacting to sound (almost 100%). Others showed considerable ignorance about neonatal responsiveness; mothers and fathers varied significantly but at least 13% of both partners held serious misconceptions, chiefly about babies of up to a week old (table 2).

Experience—The only significant difference brought about by experience (corrected for continuity) was the expected onset of smiling. Overall 47.9% (312/652) parents expected responsive smiles by 6 weeks. When considering 4 weeks as an alternative, inexperienced parents (mothers 16.8%, 36/214; fathers 22.0%, 27/123) more than experienced ones (mothers 8.0%, 16/200; fathers 10.6%, 12/113), expected smiles by then: $Z=2.56$ (mothers); 2.17 (fathers), $p<0.05$.

POSTNATAL INQUIRY

Responsiveness—Thirty percent of parents noted general responsiveness within a week, the mean time for observation of specific responses (visual, auditory, smiling) being later (table 3). Matching a couple's antenatal and postnatal

Table 3 Baby's postnatal responses first observed by parents

	Mean (SD) (weeks)	Median	Quartiles
Used eyes	2.90 (2.49)	3	1, 4
Enjoyed talk	2.85 (2.86)	2	0, 4
Smiled responsively	4.43 (2.06)	4	3, 6

answers, there was a significant association between the postnatal recognition within a week of a baby's visual alertness and attentiveness to talk and mothers who had expected this antenatally: for *visual* interest, χ^2 1 df=9.88, $p<0.005$ ($n=261$) and for interest in *talk*, χ^2 1 df=10.61, $p<0.001$ ($n=274$).

Smiling—The observed onset ranged from birth to 12 weeks, the mean (SD) of 4.43 (2.06) weeks differing significantly from the average 6 weeks expected by parents antenatally: $Z=-12.70$, $p<0.001$ ($n=277$).

Crying babies—Parents antenatally had selected causes of crying from a list; postnatally they made their own speculations. Antenatally and postnatally 100% of parents thought that babies cry for physical reasons such as hunger. Antenatally 86.8% (360/415) of parents but only 77.3% (214/277) of parents postnatally indicated emotional causes for crying, such as loneliness or boredom. This was a significant change (using the McNemar test: χ^2 1 df=13.43, $p<0.001$).

Parents were more likely to indicate postnatally that their babies cried for emotional reasons when the mothers had been better educated (45/51, 88.2%) than when they had left school at 16 years (169/226, 74.8%); χ^2 1 df=4.29, $p<0.05$. Despite these differences, 96.8% (269/278) of all parents postnatally would try to comfort a baby by emotionally directed methods such as cuddling or talking. One father still thought postnatally that his 3 month old baby cried because 'naughty'.

Parental warmth and how to gauge it

This was attempted by evaluating P and RR scores.

Paternal interest and involvement: P scores

Antenatal—Although many mothers included information about their partners, only 58.2% fathers completed the antenatal questionnaire; 18.6% (77/413) fathers attended antenatal classes; 89.5% (365/408) wanted to be present at the birth and 90% (244/271) achieved this. One died and 10 left during the pregnancy.

Postnatal—P scores for 278 fathers ranged from P0 for 4% (now no contact), P1 for 8%, P2 for 16%, and P3 for 72%; 88.5% men who scored P3 had been at the birth.

Reciprocal regard: RR scores

Understandably, the warmth with which parents spoke about their baby's personal interest was more noticeable in postnatal than in antenatal replies. A few examples will illustrate this.

Recollections—personal and impersonal:

Q: 'What did your baby like looking at when he/she could first see?'

A: 'My face'. 'Brightly coloured objects'.

Q: 'What does he/she like looking at now?'

A: 'Mum, dad, brother', 'TV'.

Q: 'What does he/she like listening to now?'

A: 'Noises made by mouth', 'Hoover'.

Q: 'What does he/she like best?'

A: 'Our singing to him', 'Bottle and dummy'.

Warmth

Q: 'What do you find most interesting about your baby?'

A: (Original prose) 'The way he senses someone coming into the room, for example, Dad coming home'. 'The delight shown on his face every time he sees me'. 'Everything'.

Pointers to degree of reciprocal regard

Crying mothers—38.5% (107/278) of mothers postnatally admitted to crying when their babies cried. This was not related to age, parity, socioeconomic group, or education. Altogether 63.6% (68/107) who cried were breast feeding mothers as against 46.5% (79/171) breast feeders in the non-crying group: $Z=2.70$, $p<0.01$. Overall, 88.8% (246/277) mothers knew that babies cry for emotional reasons; 91.5% (97/106) of those who cried with their babies knew this as did 87.1% (149/171) who did not cry with them (this was not significant). Crying mothers tended to have higher RR scores (table 5b).

Some of the parents' replies could have reflected inarticulacy as much as lack of imagination or interest, so RR scores were compared between mothers who left school early or later and between families of different social backgrounds. This showed significant differences.

Reciprocal regard and education—All 95 mothers scoring RR3 breast fed their babies. As intent to breast feed had been associated with higher education, the distribution of RR 1–3 was compared between 227 mothers who left school early and 51 who stayed on after 17 years of age. RR scores were found to be significantly associated with the length of school attendance. In mothers who left school under 17 years 36.6% scored RR1, 33.9% RR2, and 29.5% RR3. In mothers who left school after 17 years 15.7% scored RR1, 29.4% RR2, and 54.9% RR3 (χ^2 2 df=13.65; $p<0.005$).

Reciprocal regard and socioeconomic group—Thirty three fathers were either unemployed or of unknown occupation. In the other 245 families there was a significant association between the decrease in percentage of those scoring RR3 and their descent in social status: χ^2 4 df=20.19, $p<0.001$ (table 4).

Table 4 Reciprocal regard (RR) scores and socioeconomic background. Results are number (%)

Socioeconomic group	RR1	RR2	RR3	Total
I/II	12 (4.9)	19 (7.8)	33 (13.5)	64 (26.1)
III	37 (15.1)	51 (20.8)	48 (19.6)	136 (55.5)
IV/V	24 (9.8)	12 (4.9)	9 (3.7)	45 (18.4)
Total	73 (29.8)	82 (33.5)	90 (36.7)	245 (100)

χ^2 (4df)=20.19, $p<0.001$.

Table 5 Pointers to warmth of reciprocal regard (RR scores)

	No (%)	RR1	No (%)	RR2	No (%)	RR3	χ^2 (2 df)	p Value
(a) Antenatal:								
Attended antenatal classes	44/91 (48.4)		56/91 (61.5)		63/94 (67.0)		7.01	<0.05
Father hoped for baby to breast feed	26/47 (55.3)		35/54 (64.8)		53/64 (82.8)		10.28	<0.01
Mother left school >17 years	8/91 (8.8)		15/92 (16.3)		28/95 (29.5)		13.65	<0.005
Mother left school <17 years								
(i) Intended to breast feed	31/78 (39.7)		43/74 (58.1)		42/67 (62.7)		8.80	<0.05
(ii) Aware babies like faces	55/80 (68.8)		48/77 (62.3)		55/67 (82.1)		6.92	<0.05
Parity (first baby)	47/91 (51.6)		54/92 (58.7)		47/95 (49.5)		NS	
Maternal age (young)	23/91 (25.3)		17/92 (18.5)		19/95 (20.0)		NS	
(b) Postnatal:								
Saw baby liked faces	25/90 (27.8)		36/92 (39.1)		69/95 (72.6)		40.70	<0.001
Recognised vision <1 week	17/86 (19.8)		25/89 (28.1)		46/93 (49.5)		19.23	<0.001
Paternal involvement P3	54/91 (59.3)		65/92 (70.7)		81/95 (88.0)		15.59	<0.001
Mother cries with baby	30/91 (33.0)		31/92 (33.7)		46/95 (48.4)		6.02	<0.05
Good peer support	18/91 (19.8)		28/92 (30.4)		49/95 (51.6)		21.75	<0.001
Mother left school >17 years	4/8 (50.0)		8/15 (53.3)		26/28 (92.9)		11.03	<0.005
Breast fed								
Mother left school <17 years								
(i) Breast fed	25/83 (30.1)		43/77 (55.8)		41/67 (61.2)		17.20	<0.001
(ii) Aware babies have emotional cries	50/83 (60.2)		57/76 (75.0)		62/67 (92.5)		20.51	<0.001

Other significant associations—Including a separate analysis of mothers who left school before 17 years of age and a retrospective antenatal analysis, other significant associations are documented in table 5. Parity and maternal age were not significant.

Non-responders—One hundred and thirty seven of 138 couples who had completed antenatal but not postnatal questionnaires were retrospectively analysed. There was no association with age, sex, previous parity, socioeconomic group, or education, but mothers and fathers differed.

Mothers—Altogether 65.5% (182/278) responders but only 48.9% (67/137) non-responders planned to help a baby to learn in the first week: $Z=3.24$, $p<0.01$ and 15.5% (43/277) responders but 28.7% (39/136) non-responders would try to interest a baby of under 3 months with impersonal input only: $Z=3.10$, $p<0.01$.

Fathers—Altogether 63.6% (110/173) responders but 78.3% (54/69) non-responders had previously fed a baby: $Z=2.21$, $p<0.05$, and 72.9% (124/170) responders but 88.6% (62/70) non-responders expected a baby to react to the sound of a slammed door: $Z=2.47$, $p<0.05$. Expectations of response to the mother's voice or heartbeat showed no significant difference between the two groups.

Discussion

In our technological society parents may know more about the equipment available to save neonatal life than they do about a baby's own innate abilities. Thus over half the parents surveyed agreed with the proposition that 'babies under six weeks old just feed, sleep, cry or fill their nappies'. Although many of their other answers showed more insight, a worrying cohort indicated that this could be their serious opinion.

ANTENATAL IGNORANCE

For at least 13% of parents to expect babies of 1 week old neither to enjoy looking at faces or shapes nor to enjoy conversation (table 2) means that they could miss the best period to start mutual early attachment.¹¹ For their babies

rejected overtures could provoke fretfulness or fussiness during feeds, which would normally offer such golden opportunities for face to face interaction.¹² Alternatively, babies may stop trying to interact and become withdrawn, feed badly, then fail to thrive. Either way, they are emotionally deprived and could become intellectually delayed, particularly if their parents think them to be unteachable before 3 months of age. Bored babies may cry but then be thought of as naughty. Instead of empathy this can provoke antipathy with the risk of physical abuse to follow.¹³

POSTNATAL OBSERVATION

In contrast, parents who had expected visual and auditory responses antenatally were significantly more likely to find them postnatally, reporting their baby's attentiveness, bodily movement, mouthing, or other evidence of responsiveness. A third commented on this within the first week of life. Even a mother without such anticipation noticed on her baby's first day how 'She gazed at me with rapt attention and her eyes followed me when I moved'.

There was no correlation between the timing of smiles expected antenatally and witnessed postnatally. Those who claimed early smiles could sound apologetic: 'It was a real smile, the health visitor saw it'. That the average postnatal observation of smiling was 4.4 weeks, not the 6 weeks forecast by about half the antenatal parents and most text books, indicates that young babies themselves can contribute to a revision of opinion. By 3 months of age most were no longer thought to cry from naughtiness, though presumably it was their own preoccupation with the physical aspects of care that tended to make parents now overlook the possibility of a baby's emotionally induced distress.

THE IMPORTANCE OF FATHERS

It was encouraging that 90% fathers were present at delivery and that high P scores and RR scores were so closely associated (table 5b). Past concentration on mother-infant interaction only has tended to do a disservice to fathers; they should be welcomed to infant welfare clinics and toddler groups as well as to antenatal classes and the labour room. With the apparent exception of agreement about breast feeding, the attitudes and opinions of fathers are usually important to their partners, as the multiparous women in this survey showed by citing them as their 'advisers in chief'. It is, therefore, important to ensure somehow that fathers as well as mothers become correctly informed about early responsiveness from babies (see table 2). As the group of non-responders also showed, both parents need to be told how they prefer personal to mechanical stimulation. Professional advisers might hope to encourage fathers in this but unless from a higher socioeconomic background these men found advice from professionals less acceptable than from their own older generation; few of the fathers

studied attended antenatal classes. Man to man teaching or more input from the media (including hospital booklets which most read) may be less threatening so more effective.

LEARNING BY EXPERIENCE

It is often assumed that multiparous women are more likely than others to know about the needs and skills of babies. This was not evident in the areas covered by this study. There was a surprising sameness in the expectations of first time and experienced parents. The mother's antenatal expectation of a baby's innate ability was, for both groups, a more important influence than parity in the correctness of parents' postnatal observations. Ignorance may be reinforced without insight.

It follows that grandparents, from whom young parents often seek advice, may also still need enlightenment. As information about neonatal responsiveness has only been documented in detail during the last two decades, the older generation, unless naturally good at observation, may not stress a baby's need for personal interaction. The myth of windy smiles is still perpetuated,¹⁴ although admittedly by some professionals as well as by grandmothers: this may explain the reporting of later smiles in babies of experienced parents. (Why babies should be thought to smile with wind when nobody else does remains an unsolved mystery.) The mothers of younger, poorer, early school leavers may well have bottle fed their own babies so could influence their daughters to do the same. Unfortunately, some who consider themselves to be experienced can become unteachable.

RECIPROCAL REGARD, EDUCATION, AND DISPOSITION

Attentive observation of and response to a baby may overthrow antenatal ideas. Thus a mother, adamant that she did not plan to breast feed, reported how the baby had helped to change her mind. 'Almost from birth she was clearly able to focus on my face at close range and smiled at three weeks old'. In watching their baby, from birth, start to learn and to interact her parents had themselves been captivated and instructed. 'Most interesting' to them at 3 months was 'the fact that she tries to carry on a conversation, both with voice, eye contact and gestures and is obviously often "telling" you something'. RR scores were boosted by such warm reporting of mutual rapport between parents and child.

As the assessment was on paper, not in person, the greater fluency of educated minds could itself have affected the scores, though not necessarily so. 'He talks to me and he always smiles, he smiles at everyone he talks to him he is so pleasant' exemplifies sentiment more than scholarship. Better educated mothers tended to have a higher RR score and were more readily attuned to a baby's crying for emotional reasons, as well as being more likely to breast feed. However, breast feeding and sympathy for a baby's emotional distress were also associated with high RR scores among the subgroup of

early school leavers (table 5b). Warmth is more a matter of disposition than of a trained mind. Maternal sensitivity was shown particularly by breast feeding mothers with a higher RR score who were more likely to cry with their babies, but educational and social backgrounds were unrelated.

The low score of RR1 was commoner among early school leavers. It was associated both with parents' failure to observe early vision in the baby and their having failed to report support from their peers. These mothers were also less likely to cry when their babies cried. Such parents may simply not relate easily or well to many other people, including babies. A poor RR score may thus have wider implications for the stability of a partnership, the perpetuation of social isolation, and the emotional deprivation of children's children. As it may reflect poor parenting it is important to teach and encourage each generation of potential parents to enjoy warmer rapport, not only with babies. That parents with higher RR scores already had warmer personalities tallied with their higher paternal scores and the value that they placed on advice from friends.

POINTERS TO RECIPROCAL REGARD OR ITS ABSENCE: HOW TO PROMOTE IT

Retrospective review of the antenatal replies of those scoring RR3 shows similar pointers for their subsequent warm interaction with the baby (table 5a). Expressed conversely, regardless of maternal age or parity, parents less likely to have it did not attend antenatal classes, had no interest in breast feeding, and the mothers were likely to have left school early. This compares with at risk groups described by other workers.¹⁵⁻¹⁷ However, there was more antenatal hope of postnatal warmth if a less educated mother knew that babies enjoy faces and if both parents intended their baby to breast feed.

NON-RESPONDERS

These parents had shown antenatally a more impersonal attitude to the baby, independent of age, education, or socioeconomic group. Such mothers, regardless of parity, did not expect early learning. Neither did they plan to offer much personal interaction to a 3 month old baby (such as talking, tickling, playing) but instead suggested that babies would like toys, bright lights, record players, or other objects. Their partners, although with a greater previous experience of babies, emphasised their responsiveness to mechanical sounds.

PROMOTION OF RECIPROCAL REGARD

All parents, including the non-responders, had willingly participated in the antenatal questionnaire and most of the men had intended to be there at the birth. They could equally well have cooperated therefore if personally invited to watch a demonstration of parent-baby interaction in the waiting area. Waiting time could thus have become learning time.

One of the last postnatal questions asked

parents if their baby had taught them anything and if so, what? Answers ranged from 'What hard work they are' and 'How much patience you need', to indications that, despite any difficulties, mutual reciprocal regard had become high. One fluent mother, recording how her husband shared totally in the baby's care apart from breast feeding ('and that's not his fault') said, 'She's taught me patience and also how it is possible to be absolutely devoted to someone without regard for anything else—I'd lay down my life for her which is quite frightening really'. Such parents are unlikely to be found among child abusers and such babies are likely to thrive, both physically and emotionally.

CONCLUSION

Being a warm, responsive parent may not come naturally. Even those who do not attend antenatal classes evidently find help from relevant educational booklets, which should therefore be well prepared and widely available. Simple educational input, from primary school onwards, could bring hope of better parent-child attachment. Seeing a baby's face to face interaction, even on video, could encourage belief and behaviour at all ages and in a variety of venues. The widespread use of audiovisual aids is important in an increasingly illiterate society. Ultimately, the best tutorials come within the family circle, but those concerned need first to be attuned.

Those offering antenatal or postnatal care and counsel need to teach not only the mechanics of physical care, including breast feeding, but also the innate potential of babies from birth onwards for engagement in responsive relationships. Some things are better caught than taught. By showing their own enthusiasm and concern, care givers (including informed grandparents) may inspire even experienced parents, together with their other children, to tune in to newborn babies with much greater expectancy than they may otherwise display. Encouraging parents to expect a newborn baby to want early eye to eye contact and conversation and for them to respond to this could be to release

warmth and understanding. It could also give the baby a personal opportunity to become the most competent teacher of all.

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Inherited metabolic diseases in the sudden infant death syndrome

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Abstract

All sudden, unexpected infant deaths presenting during a two year period within a defined geographical area in Avon and north Somerset were investigated for inherited metabolic disease. Of 95 deaths, 88 were classified as cases of sudden infant death syndrome (SIDS). In addition to the normal postmortem investigations, samples of cerebrospinal fluid, urine, vitreous humour, and skin were collected for metabolic studies. No abnormal organic acid metabolites were found in the fluids from the 88 cases of SIDS. Fatty acid oxidation was assessed in skin fibroblasts from 70 cases of SIDS, but no examples of medium chain acyl CoA dehydrogenase (MCAD) deficiency were found. One case with abundant glycogen in the liver was subsequently diagnosed as having glycogen storage disease type 1c. These findings suggest that the incidence of MCAD deficiency and other metabolic diseases in SIDS is much lower than previously claimed.

A link between sudden, unexpected, infant deaths and inherited metabolic diseases was made almost 30 years ago,¹ but there has been increased interest in this topic recently.² In particular, it has been claimed that an abnormality of fatty acid β -oxidation, medium chain acyl CoA dehydrogenase (MCAD) deficiency, could cause 3% of cases of sudden infant death syndrome (SIDS),³ and inherited metabolic diseases could account, in total, for about 10% of these deaths.⁴ However, these estimates were not based on systematic studies of SIDS cases and may not represent the true contribution that metabolic diseases make to the overall problem.

Inherited metabolic diseases that are known to be associated with acute life threatening events are possible causes of SIDS.⁴ The object of this study was to investigate all cases of sudden unexpected infant death within a defined geographical area over a two year period with a series of tests which should detect a large number of the relevant biochemical disorders.

Methods

During a period of two years, starting in May 1987, there were 109 babies who died suddenly and unexpectedly within Avon and north Somerset. Of these, 14 were excluded from the study because of late notification, but their omission was not considered to bias the compo-

sition of the group. The median age of the remaining 95 cases was 94 days (range 7-551) with a male to female distribution of 1.6:1. As part of the postmortem examination performed on these cases, an initial set of specimens, comprising body fluids and microbiological cultures, were obtained within a median time of 3.5 hours (range 0.25-46) from discovery of death. These specimens were processed for microbiological investigations immediately, and the remainder of the sample was frozen at -70° and stored for the biochemical tests. A skin biopsy specimen was taken for tissue culture and fibroblasts stored in liquid nitrogen at the second or third passage.

Table 1 reports the number of samples received from all 95 cases in the study. Urine was received from 54 (57%) of the patients, some of the samples obtained by squeezing out the nappy if the bladder was empty. Cerebrospinal fluid and vitreous humour was obtained in a higher proportion of babies. Skin samples were received from 80 cases and successful culture was achieved in 76 of them.

Further tissue samples were obtained at the usual postmortem examination, which followed the discovery of death by a median time of 25 hours (range 2.8-73). These tissues were investigated by a detailed histological protocol which included a frozen section of liver stained for neutral fat.⁵ As a result of the basic postmortem findings the cause of death of seven cases in the study was considered to have been fully explained, while the remaining cases were classified as SIDS. However, the metabolic investigations were performed in all 95 cases in the study as far as adequate specimens were available.

Urine, cerebrospinal fluid, and vitreous humour were examined by gas chromatography/mass spectrometry (GC/MS) for organic acid metabolites⁶ and by thin layer chromatography (TLC) for amino acids.⁷ These are standard methods for detecting inherited metabolic diseases in the urine of living patients, GC/MS covering a wide range of fatty acid oxidation defects, organic acidurias, and some urea cycle disorders. It has been confirmed that a number of these diseases may be detected by the accumulation of abnormal metabolites in vitreous humour and cerebrospinal fluid obtained after death.⁸⁻¹⁰ Similarly, TLC of these body fluids should detect all amino acidopathies and the urea cycle disorders that have increased amino acid concentrations. Available serum samples were analysed for free and total carnitine by a standard radioenzymatic method,¹¹ as a possible means of screening for organic acidurias.

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Patients with organic acidurias tend to have low free carnitine concentrations because of an increased acylation of carnitine. A finding of low free carnitine, or an increased ratio of acyl to free carnitine, would indicate the need for more detailed investigation for an organic aciduria.

Cultured fibroblasts were used to measure MCAD by comparing $^{14}\text{CO}_2$ release on incubation with (1- ^{14}C) labelled octanoic acid with the release from labelled butyric acid by the method of Saudubray *et al.*,¹² as modified by G T N Butterworth and J Besley (personal communication).

Results

The number of specimens in which the various analyses were performed are shown in table 1. Priority was given to GC/MS as it was considered to be the most likely to yield positive results. In all, 94 infants were investigated by GC/MS in at least one body fluid but no indication of a specific abnormality was found in any of the samples. There was a peak of acetylaspartic acid in 25 (59%) of the cerebrospinal fluid specimens. A similar abnormality has been reported in Canavan's disease,¹³ a hereditary condition that is associated with spongy degeneration of the brain. There were no histological changes suggestive of this disease in our cases and it is almost certain that our finding was due to postmortem changes of no particular diagnostic importance.¹⁰ There were no abnormalities in the TLC of amino acids.

Carnitine was determined in 52 serum specimens (table 2), of which 47 were in the SIDS category and five were explained. Concentra-

tions of free and total carnitine were grossly raised in most samples compared with reference values for live babies of similar age, whereas the ratios of acyl to free carnitine were comparable. There was no apparent difference between the explained deaths and the SIDS cases.

Table 3 gives the results of the skin fibroblast studies to diagnose MCAD deficiency. There was no difference between the results of 70 infants classified as SIDS and six in the explained death group. On the other hand, fibroblasts from four children not in the study, but diagnosed in our laboratory as having MCAD deficiency by GC/MS of urine and by other metabolic findings, showed a significant reduction in $^{14}\text{CO}_2$ release with labelled octanoic acid as substrate. Table 3 shows a large standard deviation in all groups and there was an overlap in the distribution of the MCAD and the sudden death patients. However, this was due to a wide variation between batches in the assay, and within a batch patients with fatty oxidation defects were clearly differentiated.

Two livers have shown very striking panlobular microvesicular fatty changes comparable to those in Reye's syndrome, although no metabolic abnormality was found.

Discussion

Our investigation of organic acids in urine, cerebrospinal fluid, and vitreous humour in 94 cases of sudden infant death, including 88 with SIDS, failed to detect any abnormality. In addition, there was no indication of MCAD deficiency in the 70 SIDS cases in which it was looked for specifically using skin fibroblasts. A deficiency of MCAD can be diagnosed usually both by the urinary organic acid profile and by the skin fibroblast methods. In all, 69 SIDS patients had both types of investigation and showed a concurrence of negative results. An almost identical study to our own, on 105 cases of SIDS, also produced negative results.¹⁰ The number of patients we investigated by TLC of amino acids was rather limited, but a published study of quantitative amino acid concentrations on the vitreous humour of 120 SIDS patients failed to find any disorder.¹⁴

It has been suggested that the increase in serum carnitine observed in sudden infant death (table 2) is a postmortem change, because a correlation between carnitine concentration and the interval from estimated time of death to blood sampling has been found (P Divry, personal communication). Our data showed a similar tentative correlation. The estimated time of death was calculated as the mid-point in the time interval from when the baby was last known to be alive to when it was found dead. Babies were included in the analysis when this time interval was less than six hours ($n=36$). The correlation between the plasma free carnitine and the time from the estimated death to the blood sample being taken gave a linear regression equation, $y=36.1+24.4x$ ($r=0.61$, $p<0.001$). For plasma total carnitine the regression equation was $y=91.4+25.7x$ ($r=0.67$, $p<0.001$). It seems probable that the post-mortem rise in serum carnitine would mask a

Table 1 Samples received and analysed from 95 cases of sudden infant death

	Cerebrospinal fluid	Urine	Vitreous humour	Blood	Skin
Samples received	77	54	84	55	80
Samples analysed					
Organic acids (by GC/MS)	42	47	84	—	—
Amino acids (by TLC)	12	5	0	—	—
Carnitine in serum	—	—	—	52	—
CO_2 release from octanoate in skin fibroblasts	—	—	—	—	76

A blank indicates that the assay was not applicable in the type of sample.

Table 2 Free and total serum carnitine concentrations in 52 cases of sudden infant death. Results are mean (range)

	No of babies	Free carnitine ($\mu\text{mol/l}$)	Total carnitine ($\mu\text{mol/l}$)	Ratio acyl*/free carnitine
Sudden infant death	52	169 (66–550)	235 (79–620)	0.42 (0.12–0.76)
Reference values ¹¹ (babies aged 8 days–1 year)	25	33 (15–51)	44 (19–68)	0.36 (0.11–0.65)

*Acyl=total–free carnitine.

Table 3 Medium chain acyl CoA dehydrogenase activity in skin fibroblasts (nmol/h/mg protein). Results are mean (SD)

	No of babies	$^{14}\text{CO}_2$ release from octanoate	$^{14}\text{CO}_2$ release from butyrate	Ratio octanoate/butyrate oxidation
SIDS	70	1.43 (0.57)	2.84 (0.85)	0.50 (0.14)
Explained sudden death	6	1.15 (0.60)	2.56 (1.02)	0.46 (0.18)
Known MCAD	4	0.47 (0.14)	2.76 (0.79)	0.17 (0.05)

There is a significant difference between the SIDS and MCAD deficiency cases for $^{14}\text{CO}_2$ release from octanoate ($p<0.01$) and for the ratio of octanoate to butyrate oxidation ($p<0.001$).

free carnitine deficiency that should indicate the presence of an organic aciduria. However, table 2 shows that the ratio of acyl to free carnitine remained normal in our sudden death patients and therefore it is possible that a high ratio could successfully indicate an organic aciduria. This hypothesis could only be tested when positive cases of organic aciduria are found in SIDS.

The results reported here and by others^{10 14} suggest that the incidence of MCAD deficiency and other metabolic diseases in SIDS is very much lower than previously estimated. Despite this, it is important to identify the rare cases in which inherited metabolic disease is the cause of death. Routine screening of all sudden infant deaths may not be justifiable and some means of concentrating investigations of those babies with a higher likelihood of having an underlying metabolic disease would be valuable. The acute episode in a metabolic disease is almost always preceded by a short illness with febrile, particularly gastrointestinal, features which affects regular food intake. Unfortunately, similar signs of illness are described in the week before death in many SIDS cases, notably in two thirds of the babies included in our study.¹⁵ The finding of panlobular microvesicular fatty changes in the liver at postmortem examination is another factor which needs to be considered. It may suggest the presence of a metabolic disorder before death, but it is not a specific indication of this¹⁶; nor it is clear that the absence of liver fatty changes rule out the possibility of a metabolic disease.¹⁷ One has to conclude that there are no satisfactory indicators of inherited metabolic disease in SIDS cases apart from the rare circumstances of the unexplained death of a sibling.

Since the completion of this study, interest was aroused by a report linking glucose-6-phosphatase deficiency (glycogen storage disease type 1, GSD 1) with sudden infant deaths.¹⁸ One of the patients in our study was noted to have an unusually high lactic aciduria and abundant glycogen in the liver. This case has now been diagnosed as GSD 1c by A Burchell

(personal communication). Liver from all cases in our study has now been investigated for GSD 1, with a negative result.

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Transoral decompression and posterior stabilisation in Morquio's disease

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Abstract

A 3.5 year old boy with Morquio's disease was referred with a persisting left hemiparesis four months after a fall and was found to have craniocervical junction compression due to atlantoaxial subluxation and significant anterior soft tissue compression. Transient unconsciousness at the time of the fall was probably due to medullary concussion as a result of hyperextension, not a head injury.

Spinal cord compression due to atlantoaxial subluxation at the craniovertebral junction is a major cause of disability and death in these patients. Once cervical myelopathy appears, early posterior occipitocervical fusion has been advocated in order to arrest the progression of neurological disability and this is successful in most cases. This conventional approach was considered unsafe because of the significant anterior compression. A combined anterior transoral decompression with posterior fusion to deal with this particularly difficult problem is described.

Morquio's disease (mucopolysaccharidosis type IV) is an inherited connective tissue disorder caused by absence or reduction in activity usually of one of two ubiquitous lysosomal hydrolases, *N*-acetylgalactosamine 6-sulphatase (MPS IV type A) and β -galactosidase (MPS IV type B).¹ It manifests clinically as a disproportionate dwarfing dysplasia with hypermobility of the joints due to laxity of restraining ligaments and numerous other features. Cardiac defects and spinal cord compression are major causes of disability and death. Spinal cord compression in the thoracolumbar and sometimes also in cervicothoracic regions is due to kyphosis and narrowing of the spinal canal and is usually less severe there than at the craniovertebral junction where localised soft tissue thickening is the dominant compressing agent.² Prompt posterior occipitocervical fusion is advocated once clinical myelopathy is present³ and this procedure may result in regression of thickened soft tissue.² However, most authorities agree that established neurological deficits usually do not improve, and operative mortality can be high.^{3, 4}

Modern computed imaging (computed tomography and magnetic resonance imaging) has emphasised that in some patients there is so little available space for the spinal cord, that posterior fusion may be hazardous; this suggested the logic of performing a prior anterior decompression. Moreover, immediate decompression of the spinal cord by this procedure might allow neurological recovery to take

place. The authors describe a case managed in this way.

Case report

A boy was born after an uneventful pregnancy and delivery. There was no known consanguinity and his parents and other siblings were normal.

At birth he was noted to have a pigeon chest deformity, and during his early development he was of short stature and physically weak. He did not have any of the ocular or cardiac manifestations of Morquio's disease. Although his early developmental milestones such as sitting, smiling, and talking were normal and comparable with those of his siblings, he did not start to walk until the age of 2.3 years. Shortly after his third birthday he had a fall, and although he did not hit his head he was unconscious for a short period. On regaining consciousness, he was intellectually intact but had a left hemiplegia and was unable to walk. Plain radiographs revealed atlantoaxial subluxation, and he was placed in a soft collar. There was a gradual improvement in function but he had a residual left hemiparesis. He was able to sit, crawl, and grasp things with his left hand but was unable to stand or walk, and so, four months after the injury at 3.5 years, he was referred for consideration of decompression and stabilisation of his craniovertebral junction.

On examination he was short statured, with a prominent cranium and vault, pigeon chest deformity, and kyphoscoliosis. He had spatulate fingers and hypermobile joints. His mental development was normal for his age. His cranial nerves were normal. He was unable to stand and tended not to move his left arm, holding it in flexion most of the time. He had a left hemiparesis, but power was normal on the right. Tone was increased in the left arm and leg. Reflexes were generally brisk, more so on the left, with extensor plantar response on that side. There was no detectable sensory deficit and autonomic function was normal.

His corneas were clear, there was no evidence of cardiomegaly or cardiac valvular dysfunction, and abdominal examination was normal.

Computed tomographic myelography demonstrated appreciable compression of the spinal cord by thickened soft tissues in the region of the partly ossified odontoid, associated with atlantoaxial subluxation (figs 1 and 2) which reduced in extension, although this did not completely relieve the compression (figs 3 and 4).

Skull halo traction was used to give preliminary reduction then transoral excision of the

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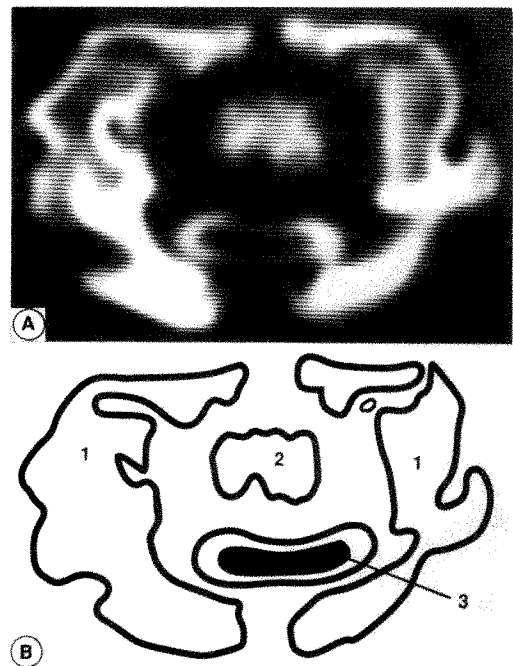


Figure 1 Axial computed tomographic myelogram (A) and line diagram (B) through the craniovertebral junction, showing compression of the spinal cord in flexion by the soft tissue surrounding a malformed odontoid process and anterior arch of atlas. 1=lateral mass of C1, 2=odontoid base, 3=spinal cord.

odontoid, the body of C2 and the adjacent soft tissue elements compressing the spinal cord was performed, followed by a posterior occipito-cervical fusion with a bone graft obtained from femur and tibia.

His recovery was uneventful. The halo body jacket was removed after six weeks, and his left hemiparesis improved considerably.

The histopathological examination of the excised tissue showed it to be composed of reactive tissue and partially ossified bone, with no evidence of abnormal mucopolysaccharide deposition.

Discussion

Abnormal development at the craniovertebral junction is an important feature of Morquio's disease. Plain radiographs of this region are often difficult to interpret⁵ and the following synopsis is based on more reliable observations made by computed myelography.^{2,6} In Morquio's disease, the odontoid process is detached from its basal portion and ossifies late, the atlas ring is small with an abnormally thick neural arch, and midline fusion defects are usually present. Although both anterior and posterior atlantoaxial subluxation are demonstrable, they seldom are severe and the bony spinal canal

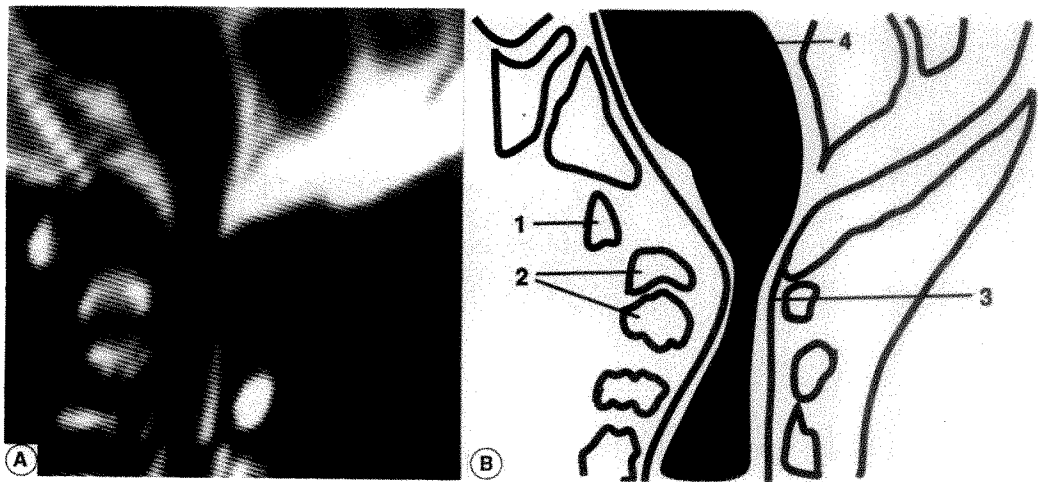


Figure 2 Sagittal computed tomographic myelogram (A) and line diagram (B) showing atlantoaxial subluxation, hypoplastic odontoid process, and soft tissue elements compressing the spinal cord. 1=C1, 2=odontoid base and body of C2, 3=cerebrospinal fluid around compressed cord, 4=fourth ventricle.

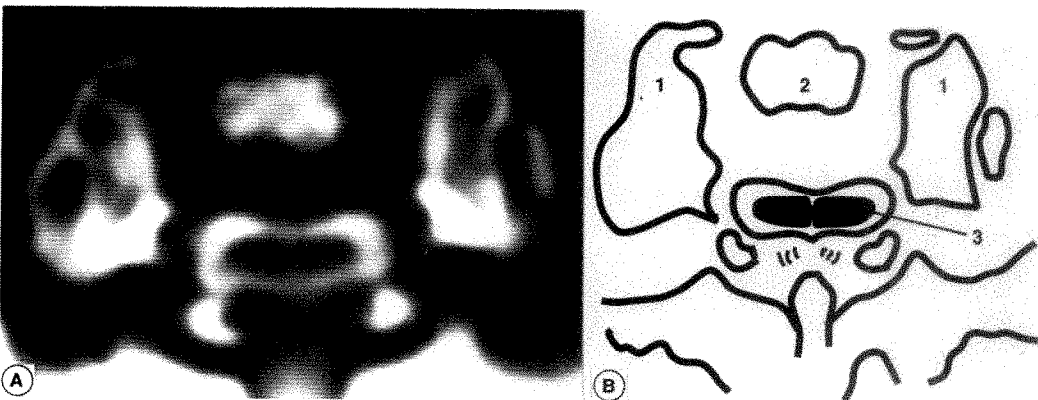


Figure 3 Axial scan (A) and line diagram (B) of the same area in extension, showing that the compression is reduced. 1=lateral mass of C1, 2=odontoid base, 3=spinal cord.

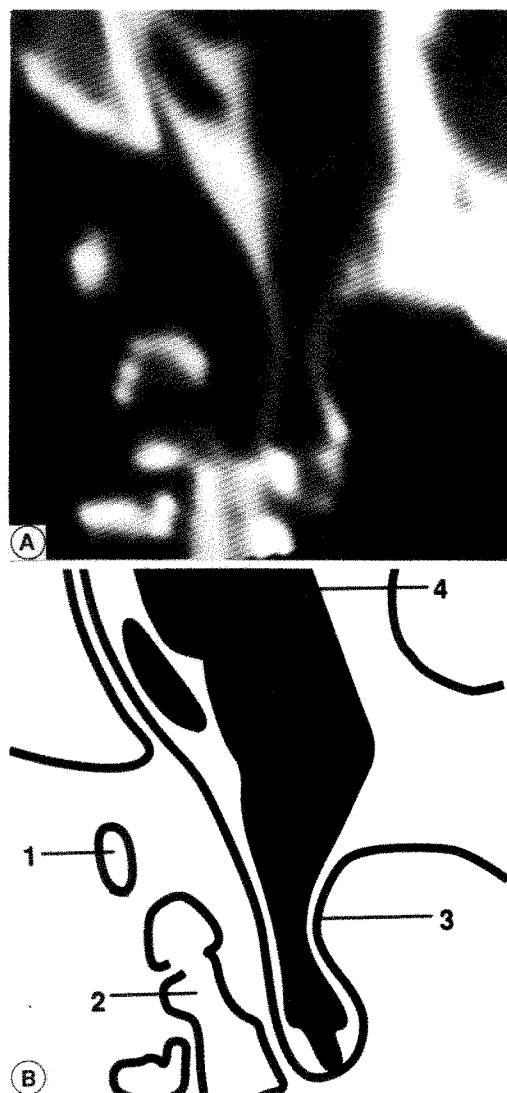


Figure 4 Sagittal computed tomographic myelogram (A) and line diagram (B) showing in extension the persisting cord deformation. 1=C1, 2=axis body, 3=cerebrospinal fluid around compressed cord, 4=fourth ventricle.

remains relatively wide. Nevertheless, spinal cord compression of some degree is present in most cases, and is severe in about 50%. The cause is narrowing of the available subarachnoid space mainly by thickening of the anterior extradural soft tissues, especially in the region of the odontoid, accentuated in some cases by mild occipital condylar hypoplasia which permits the posterior arch of C1 to invaginate the foramen magnum. In cases with mild or minimal compression, the soft tissue thickening is relatively slight; in the main it represents unossified cartilage in vertebral bodies and odontoid, which usually ossify after occipitocervical fusion. In cases with severe compression, the soft tissue thickening encroaches further into the spinal canal and consists in part of reactive ligamentous tissue with or without abnormal deposition of mucopolysaccharide.

The onset of clinical myelopathy in these patients is usually insidious, lack of endurance of physical exertion frequently being its earliest manifestation.³⁻⁷ Subsequent progression is variable, often with periods of sudden severe

functional loss which cannot always be related to trauma. Generally, progression is slower in older patients,³⁻⁹ often remaining undetected for long periods, and is more difficult to arrest or reverse by operation. A sudden hyperextension movement, as in a fall, may cause spinal cord injury of ranging severity or even medullary dysfunction leading to respiratory arrest. We believe our patient was unconscious due to concussion of the medulla rather than because of a head injury. Motor deficit without a sensory loss is also well recognised in upper spinal cord injury.

Posterior occipitocervical fusion appears to be a satisfactory method of arresting the downward clinical course in the majority of cases.^{3-4,10-11} However, once quadriplegia is established little improvement results,⁸ and where compression is severe there is a risk of precipitating sudden deterioration during anaesthesia and surgery.^{9,12-13} The need to flex the neck during the fusion procedure encourages anterior atlantoaxial subluxation and further reduces the available subarachnoid space.

There are three advantages of an initial transoral excision of the anterior extradural soft tissue elements in patients with severe compression. (1) The operation is performed with the head extended, a position in which any anterior atlantoaxial subluxation is reduced and usually the available subarachnoid space maximised. (2) Adequate decompression permits safer posterior fusion. (3) Excision of the anterior soft tissue mass often is the *only way* of achieving immediate decompression of the spinal cord, thereby increasing the chances that even an established deficit might improve. We believe all three advantages were demonstrated by our patient. While it is conceded that transoral surgery adds significant surgical trauma to an already extensive procedure, in practised hands it extends the operation time by little more than an hour. In a wide range of pathology, intraoral excisions have healed rapidly with low risk of infection and morbidity.¹⁴⁻¹⁵

In conclusion, patients with Morquio's disease and mild spinal cord compression requiring operation are probably best treated by a posterior occipitocervical fusion. Patients with severe spinal cord compression, on the other hand, may require anterior decompression before safe stabilisation can be performed by the posterior approach, and this also may offer a better chance of reversing the established neurological deficit.

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Oculocerebrorenal syndrome of Lowe

This X linked recessive disorder has been mapped to the long arm of the X chromosome (Xq 24-26). Its three cardinal features are congenital cataracts, cognitive impairment, and renal tubular dysfunction. Other clinical features include hypotonia, glaucoma, and joint swellings. Eighty two patients with this syndrome are known to the American Lowe's Syndrome Association and 15 of those together with an additional eight are the subjects of a recently published study from the National Institutes of Health in Bethesda, Maryland (Lawrence R Charnas and colleagues, *New England Journal of Medicine* 1991;324:1318-25).

Nineteen of the 23 patients were aged less than 17 years, the youngest being 4 months old. The other four were over 22 years old, the oldest being 31.

Weight and length were normal at birth and in infancy but growth slowed from the age of 2 or 3 years, weight following a curve below but parallel to the third centile and height following a line which fell progressively away from the third centile. Growth often continued well beyond the normal age but the mean final height of the four adult patients was below the third centile. Head circumferences were within the normal range. With increasing age bone age lagged progressively further behind chronological age and height age behind bone age so that bone age was between chronological age and height age.

Serum creatinine appeared to increase stepwise with age, increasing fairly dramatically in patients over the age of 15 years. In 10 patients aged under 10 years the serum creatinine ranged from 27 to 53 $\mu\text{mol/l}$. Between 10 and 15 years the range was 62 to 80 and after 15 years, 115 to 292 $\mu\text{mol/l}$. The authors suggest that renal failure in Lowe's syndrome will occur at around the age of 36 years but that seems a fairly tenuous suggestion from the data presented.

Urine osmolality was low in 21 of the 23 patients and all but one had proteinuria. In 15 patients urine protein excretion was in the nephrotic range ($>1.0 \text{ g/m}^2/\text{day}$) but they had no other features of the nephrotic syndrome. Renal tubular wastage of potassium, phosphate, and carnitine were common. Supplements of potassium were needed by eight patients, phosphate by seven, and two received L-carnitine. Fifteen patients took oral bicarbonate or citrate. Significant glycosuria was uncommon, only two patients showing a trace of glucose on dipstick testing. The amino aciduria of Lowe's syndrome seems to be less than is seen in cystinosis with little excretion of the branched chain amino acids, leucine, isoleucine, and valine. Raised serum enzyme activities including creatine kinase lead to the suggestion that there may be mild muscle disease in this syndrome contributing to the hypotonia.

Lowe's syndrome is rare but this paper gives valuable information about prognosis and about the findings to be expected at various ages.

Complications of splintage in congenital dislocation of the hip

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Abstract

The use of abduction splintage in the treatment of congenital dislocation of the hip has an important morbidity. Six children who developed complications are presented in this paper. Sustained splintage of an unreduced hip, overcorrection of the femoral head displacement, avascular necrosis of the femoral head, full thickness pressure sores, and excessive tibial torsion may occur as a consequence of treatment. Expert supervision of abduction splintage, correct case selection, and regular review are necessary to reduce the incidence of such complications.

The treatment of congenital dislocation of the hip is associated with significant complications. Two factors that may influence their development are the method and supervision of the chosen splintage and the age of the patient at the commencement of treatment. Before the introduction of splintage, the management of congenital dislocation of the hip consisted of either traction¹ or forceful closed manipulation of the femoral head.² Closed reduction and prolonged fixed splintage in a cast was promoted on the basis that redislocation would be prevented and in some cases even the presence of hypertrophied soft tissue obstructing reduction would be overcome with prolonged pressure.³ Sustained immobilisation was associated with redislocation in splintage in 32% of cases and avascular necrosis of the femoral capital epiphysis in 50%.^{4 5}

Splints such as the Denis Browne rigid bar abduction device were originally introduced to reduce the total time spent in a cast and were not recommended for use alone.⁶ Full abduction was rigidly maintained for over nine months. Nursing and maintenance of these children was greatly improved by the introduction of lighter, removable splints of which the Von Rosen was one example. This device consisted of malleable aluminium strips covered in washable rubber and applied around the shoulders, trunk, and thighs.⁷

The association between compressive vascular injury of the femoral capital ossific epiphysis and forced abduction of the hip was supported by cadaver angiographic studies demonstrating significant vascular compromise in the 'frog' position commonly used in rigid abduction splints.⁸ Experimental avascular necrosis was reproduced by immobilising the hip joints of immature pigs in plasters in full abduction after artificial adductor shortening.⁹ This awareness led to a preference for a splint

which utilised hip flexion to site the femoral head and gradual natural abduction to overcome adductor contracture. The most popular dynamic splint remains the Pavlik harness.

The Pavlik harness was introduced in 1944 and consisted of an adjustable circumferential abdominal band with crossed posterior straps and leg stirrups. The straps were adjusted to provide hip flexion and free abduction. Pavlik reported an 84% success rate with no avascular necrosis.¹⁰ Suitable modifications in the treatment protocols have produced success rates of 90 to 99% with no avascular necrosis.^{11 12} However, important complications have also been reported from the widespread use of this harness. Avascular necrosis has been reported to be as high as 28%.^{13 14} Failure to achieve reduction and redislocation¹²⁻¹⁵ as well as nerve and skin complications have been reported.^{11 12 15}

The decision to apply splintage early or delayed is controversial and may influence the development of complications, especially avascular necrosis. Early splintage was advocated in 1929 by Putti who recommended cushioned abduction as soon as the diagnosis was apparent.¹⁶ Putti recognised a group which underwent 'spontaneous reduction' and did not require treatment. Early treatment was encouraged in order to avoid the complications of delay, which included difficult reduction and an increase in the incidence of avascular necrosis.^{11 12 17 18} Others have reported avascular necrosis to be higher during treatment in the first six months of life when the developing capital epiphysis is most vulnerable to pressure.¹⁷⁻¹⁹ Barlow's observation that 60% of unstable hips would resolve spontaneously further behoves those who choose to splint all unstable hips at birth to ensure that 'normal' hips do not sustain a compressive vascular injury with subsequent proximal femoral growth plate damage and deformity.²⁰

Case histories

CASE 1 (OVERCORRECTION OF FEMORAL HEAD DISPLACEMENT)

A girl delivered normally was found to have an unstable right hip on examination. Splintage was commenced on the fourth day in a Pavlik harness and she was reassessed clinically at intervals of three weeks. Clinical examination at 6 weeks of age did not detect any abnormality but a radiograph suggested that the right hip was positioned wide of the acetabulum. An arthrogram confirmed overcorrection with the development of a large superior pool (fig 1). At

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Figure 1 Case 1 (overcorrection of femoral head displacement). Arthrograph of the right hip in a 6 week old girl. Note the inferior position of the overcorrected femoral capital epiphysis and superior pooling of the contrast medium.



Figure 2 Case 2 (epiphysitis). Pelvic radiograph of a girl aged 2 years. There is a delay in ossification of the left capital femoral ossific nucleus with some fragmentation; this appearance is suggestive of avascular necrosis.

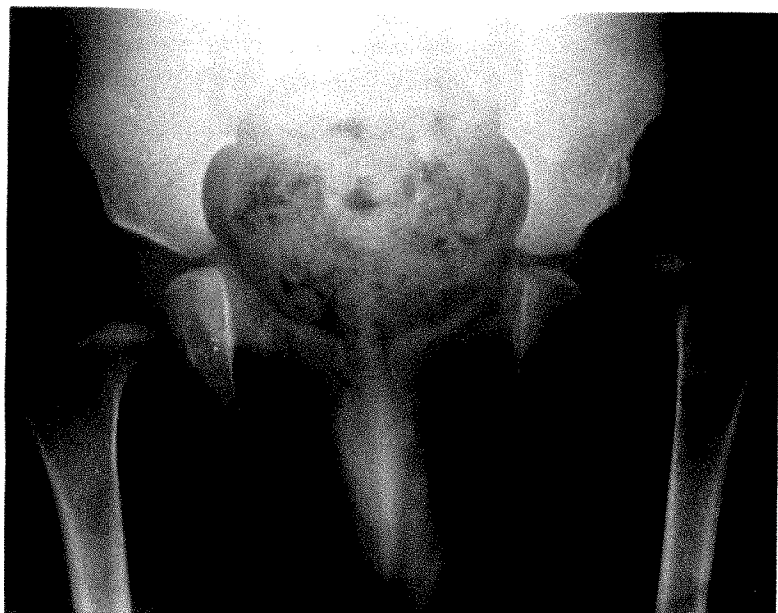


Figure 3 Case 3 (persistent hip dislocation in the splint). Pelvic radiograph of a boy at 9 months of age. This radiograph was taken after 9 months of splintage. The left hip remains dislocated.

7 months an open reduction was performed and the acetabulum was observed to be shallow. Reduction could be achieved only after considerable soft tissue resection and recovery was uneventful after six months of serial plaster spicas.

CASE 2 (EPIPHYSITIS)

A girl was born prematurely and at birth a dislocated left knee and hip were diagnosed. The knee dislocation was reduced in serial plasters and the hip was treated immediately in a Von Rosen splint. At 2 months of age the splint was causing excessive pressure around the front of the thighs and a Craig splint was applied for a further six months. The left femoral capital epiphysis was considerably delayed in development and at 2 years the radiological signs of an epiphysitis were confirmed (fig 2).

CASE 3 (PERSISTENT HIP DISLOCATION IN THE SPLINT)

A boy was found to have 'clicking' hips at birth. An Aberdeen type polythene abduction splint was applied for nine months during which time he was reassessed regularly. At 9 months of age the left hip was found to be dislocated (fig 3). At 11 months an open reduction was necessary, but the dislocation persisted. Redislocation continued to occur because of a shallow acetabulum and stability could not be achieved even after a Pemberton pelvic osteotomy (fig 4). Persistent anterior acetabular deficiency required a further acetabuloplasty and a derotation femoral osteotomy.

CASE 4 (FULL THICKNESS PRESSURE SORE)

A girl delivered normally was diagnosed as having clinical bilateral hip instability at birth. A Von Rosen splint was applied and the parents instructed that it should not be removed until the child was reassessed. Three weeks later a red pressure area was noted over the right iliac crest posteriorly. Although the lesion was dressed and the splint changed to an Aberdeen type polythene abduction splint the lesion ulcerated (fig 5). At three years of age she is clinically normal but has a 2 cm by 1 cm full thickness scar at the site of the ulcer.

CASE 5 (FAILURE OF FEMORAL HEAD RELOCATION)

A girl was born by caesarean section and diagnosed as having 'clicking' hips at birth. She was treated in double nappies until 6 weeks of age and subsequently a Pavlik harness was applied. The mother was instructed to remove this for bathing. At 4 months the harness was clearly too small and incorrectly applied with the abdominal strap below her waist. A radiograph demonstrated that the left hip had not been concentrically reduced. Successful reduction was achieved with a larger, correctly fitted harness. Treatment was continued in this for a further six months.

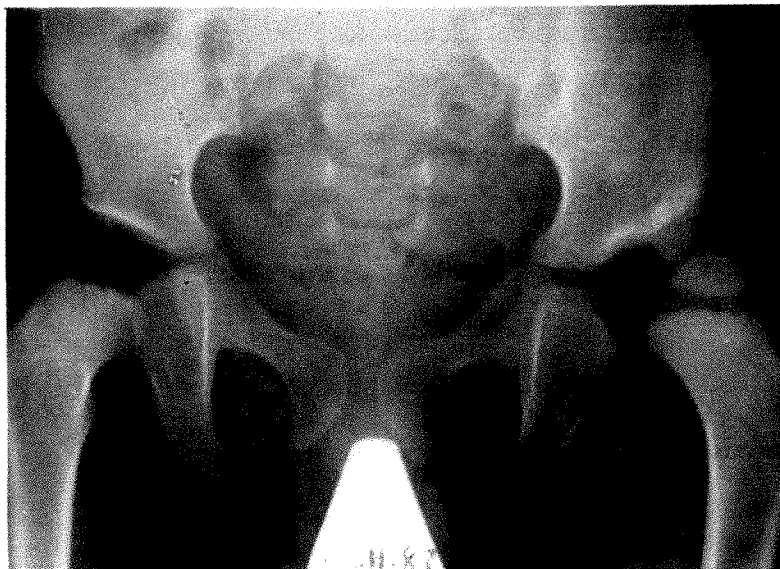


Figure 4 Case 3 (persistent hip dislocation in the splint). Pelvic radiograph of case 3 after a Pemberton pelvis osteotomy. The left hip remains dislocated. Note also delayed ossification of the right femoral capital epiphysis.

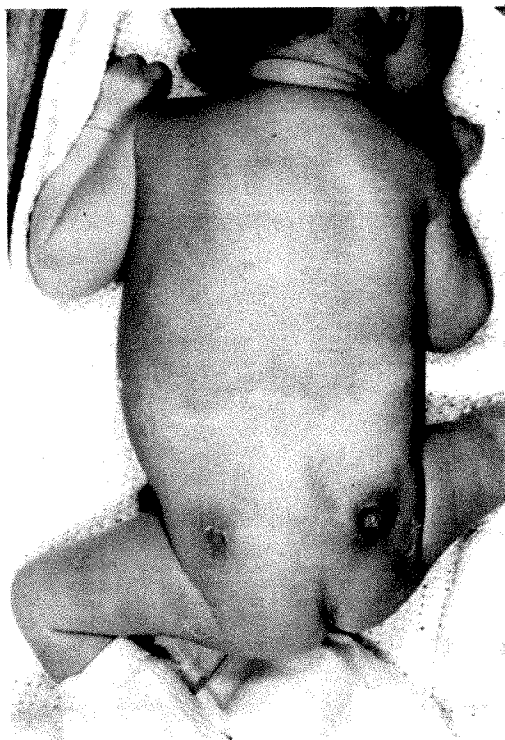


Figure 5 Case 4 (full thickness pressure sores). Girl at 3 weeks of age shortly after the removal of a Von Rosen splint. The full thickness pressure sores seen here eventually healed but large scars remain at 3 years of age.

CASE 6 (EXTERNAL TIBIAL TORSION)

A boy born in another country was noted to have a dislocatable left hip at birth and was treated in a Pavlik harness for six months. At that time the child's father was concerned that an 'ankle strap' which had been added to the splint was exceptionally tight and was turning the left leg out excessively. Splintage was continued for 11 months. At the age of 5 years, there was a 60 degree external rotation deformity of the tibia confirmed by computed tomography. The right leg is normal.

Discussion

These cases illustrate that treatment of neonatal hip instability does have a significant complication rate. The initial dilemma of those who treat this condition is whether to splint all unstable hips or whether to delay splintage on the basis that many hips will stabilise spontaneously. Advocates of immediate splintage have a special responsibility to ensure that complications are reduced as it is possible that a treated hip would have spontaneously stabilised without the need for splintage.²⁰⁻²¹ Delayed splintage risks the possibility of clinical examination failing to detect displacement because the clinical signs of instability gradually resolve in the early weeks. This resolution is associated with an increasing limitation of abduction and adductor tightness. This renders the femoral head vulnerable to compressive vascular injury with forced hip abduction in a rigid abduction splint.⁹⁻²² Careful assessment is required to ensure that the hip is splinted in the reduced position. Splintage of displaced hips or those that are eccentrically reduced will predispose to complications that increase if operative reduction is necessary.²³ The likelihood of avascular necrosis is increased and this may predispose to deformity and osteoarthritis in later years.²⁴

The dynamic type of splintage (for example, Pavlik harness) reduces the risk of forced abduction and compressive vascular injury. However, the harness must be applied correctly and the posterior straps used to limit adduction across the midline rather than abduct the hips. Similarly, the position of hip flexion is critical. The hip should be flexed to just above 90 degrees.¹² Excessive flexion may result in femoral nerve palsy¹¹⁻¹²⁻¹⁵ or inferior displacement of the hip.¹⁵ Medial knee ligament instability may occur as a consequence of valgus strain applied by a medial strap slipping over the knee.²⁵ For these reasons expert supervision of an infant in a harness is required on perhaps a weekly basis. Frequent strap adjustments are required and the position of the hip checked by clinical examination and radiography to prevent persistent posterior femoral head displacement or eccentric reduction. It may be useful for the clinician to mark the straps after adjustment to prevent interference and reduce the likelihood of losing the reduction. If necessary, treatment may have to be abandoned in favour of alternative procedures such as adductor tenotomy or planned open reduction.²⁶⁻²⁹

Ultrasound has proved to be a useful adjunct to regular clinical examination of hips splinted particularly in the Pavlik harness. Where ultrasound is available the mandatory pelvic radiograph of the infant in a Pavlik harness may not be necessary.³⁰⁻³² Additionally, ultrasound may be able to detect the hips which do resolve spontaneously.³³ A delayed examination of the hips at 2 weeks of age reduces the treatment rate and assists the assessment of hip location in those cases that do require treatment.³⁴

CONCLUSIONS

Six cases of complications resulting from the use of splintage are presented. Complications may

be prevented by observation of fundamental principles. The decision to splint an infant must not be undertaken lightly. A proportion of unstable hips do become normal by 2 weeks of age and splinting a normal hip may cause vascular injury. An infant placed in an abduction splint requires regular supervision by trained specialists to prevent any relapse of instability or complication resulting from the splint itself. Excessive abduction against tight hip adductors must be avoided particularly if rigid splintage is used. Diagnosis may be improved by ultrasound examination and the supervising specialist must also be aware that in certain cases splintage may have to be discontinued and alternative treatment such as adductor tenotomy or planned open reduction performed.

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A practical method of serial bedside measurement of cerebral blood flow and metabolism during neurointensive care

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Abstract

Acute encephalopathy is a major cause of death and neurological handicap in children. The principle aims of treatment are to provide adequate cerebral blood flow for the brain's metabolic needs and to prevent intracranial pressure rising above the level at which brain herniation occurs. Rational management requires an understanding of the pathophysiological changes in cerebral blood flow and metabolism which occur. The paucity of data on this subject reflects the perceived difficulty of measuring cerebral blood flow and cerebral metabolism in children.

A modification of the Kety Schmidt technique of measuring cerebral blood flow and cerebral metabolism is described. This modification makes it possible to perform serial bedside measurements in children receiving intensive care. This method was used to perform 348 measurements in 58 children. The method was reproducible and no significant complications were encountered. The results indicated that appreciable changes in cerebral blood flow and metabolism could occur in individual patients over time, emphasising the importance of serial measurements. This technique may provide a practical means of monitoring cerebral blood flow and metabolism in very sick children receiving neurointensive care and evaluating the efficacy of treatment.

Acute childhood encephalopathy is a condition with a high mortality and morbidity.^{1 2} Various forms of treatment may be required according to the aetiology. In all cases, however, the principle aims of treatment are to maintain a cerebral blood flow sufficient to supply the metabolic needs of neurones and glial cells and to prevent intracranial pressure rising to a level liable to result in brain herniation.³

The monitoring of intracranial pressure is now an accepted technique in paediatric neurointensive care.^{4 5} However, there is no currently accepted method of performing serial measurements of cerebral blood flow and cerebral metabolism routinely at the bedside. It is often assumed that cerebral perfusion pressure (mean arterial pressure minus intracranial pressure) provides a useful index of cerebral blood flow,^{5 6} but cerebral blood flow is dependent upon both cerebral perfusion pressure and cerebrovascular resistance. Variations in cerebrovascular resistance will thus alter the relationship between cerebral perfusion pressure and cerebral blood flow. Moreover, the measurement of cerebral blood flow alone does not provide an index of

the adequacy of blood flow for cerebral metabolism. In a normal subject cerebral blood flow will be regulated in accordance with the brain's metabolic requirements but in a child with acute encephalopathy this relationship may be disturbed.

The aim of this paper is to demonstrate that, using the Kety Schmidt technique,⁷ it is possible to perform frequent serial measurements of cerebral blood flow and metabolism in sick infants and children receiving intensive care. Thus it is now potentially possible to prescribe rational treatment and evaluate its efficacy.

Methods

THEORY

The Kety Schmidt technique, the first quantitative method of measuring cerebral blood flow to be described in man, has been validated against the bubble flow meter.⁷ The method is based on the Fick principle, which states the amount of an inert tracer that is taken up by an organ is equal to the amount delivered by the arterial blood, minus that removed by venous blood in the same time period. Thus:

$$(Q_B)_u = (Q_A)_u - (Q_V)_u \quad \text{Equation (1)}$$

Where $(Q_B)_u$ is the quantity of substance taken up by the whole brain in time u , $(Q_A)_u$ is the quantity of the substance delivered to the brain by the arterial blood in time u , and $(Q_V)_u$ is the quantity removed by cerebral venous blood in time u .

The amount of tracer delivered to the brain or removed from the brain thus equals blood flow multiplied by the arterial or venous concentrations respectively. As the arterial and venous concentrations of such a tracer would vary with respect to time:

$$(Q_B)_u = TF \int_0^u (A - V) dt \quad \text{Equation (2)}$$

Where TF = cerebral blood flow (ml/min), A = arterial tracer concentration (ml/l), V = venous tracer concentration (ml/l). This can be resolved to:

$$TF = \frac{(Q_B)_u}{\int_0^u (A - V) dt} \quad \text{Equation (3)}$$

Thus cerebral blood flow (CBF) per gram weight of brain is:

$$CBF = \frac{(Q_B)_u}{W \int_0^u (A - V) dt} \quad \text{Equation (4)}$$

where W represents brain weight in grams (g).

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Kety and Schmidt applied this equation to the measurement of cerebral blood flow in adults using 10% nitrous oxide, administered by inhalation, as the inert tracer. The denominator was derived from the curves obtained by plotting arterial and cerebral venous nitrous oxide concentrations against time, being equal to the area between the two curves (fig 1). It is not possible to determine the numerator (brain concentration of nitrous oxide) in a living subject, however, if the time u is sufficient for equilibration to have occurred between brain and cerebral venous blood, then the brain tracer concentration will be equal to the partition coefficient of the tracer (the relative amount of tracer dissolved in blood and brain) multiplied by the cerebral venous concentration:

$$\frac{(Q_B)_u}{W} = S \cdot V_u \quad \text{Equation (5)}$$

Where S represents partition coefficient and V_u is the cerebral venous concentration of the tracer at equilibrium. Thus:

$$\text{CBF} = \frac{S \cdot V_u}{\int_0^u (A - V) dt} \quad \text{Equation (6)}$$

Where CBF is cerebral blood flow in ml per gram of brain per minute (ml/g/min).

The blood-brain partition coefficient for nitrous oxide has been shown to be 1.06 in man.⁸ Thus, cerebral blood flow can be obtained if the concentrations of nitrous oxide in arterial and cerebral venous blood can be measured.

The Kety Schmidt method also enables quantitative measurements to be made of cerebral metabolism. If the arterial and cerebral venous concentrations of a cerebral fuel or metabolite

can be measured, the cerebral production or consumption of the substance (cerebral metabolic rate) can be determined:

$$\text{CMR} = \text{CBF}(A - V) \quad \text{Equation (7)}$$

Where CMR is the cerebral metabolic rate in $\mu\text{mol/g/min}$, CBF is cerebral blood flow in ml/g/min, A and V are the arterial and cerebral venous concentrations of the substance in ($\mu\text{mol/ml}$).

ADAPTATION OF THE KETY SCHMIDT TECHNIQUE TO PERFORM SERIAL BEDSIDE MEASUREMENTS IN CHILDREN

Sampling of cerebral venous blood

In the original description Kety and Schmidt directly punctured the superior jugular venous bulb to obtain cerebral venous blood uncontaminated by blood of extracranial origin.⁷ Such direct puncture has since been shown to be associated with morbidity.⁹ The Seldinger technique¹⁰ was used therefore to cannulate the internal jugular vein and a catheter (18 or 20 gauge Leder cath, Vygon) was retrogradely advanced until the tip lay in the superior jugular venous bulb.^{11 12} The position of the cannula tip at the base of the skull was subsequently confirmed by a lateral x ray film of the neck.

The catheter was left in situ and perfused with heparinised normal saline (one unit of heparin per ml, rate 1–3 ml/hour); it was also connected to a pressure transducer and the pressure wave displayed continuously (Simonsen and Weel Monitor, System 8000, Triscope) principally to allow early recognition of catheter blockage.

Administration of tracer

A modified three block rotameter (air/oxygen/nitrous oxide) enabled 10% nitrous oxide to be administered via the ventilator circuit to the patient while maintaining a constant inspired oxygen concentration. During the period of nitrous oxide administration six paired, timed, blood samples (0.2 ml) were sequentially withdrawn from a peripheral arterial catheter and the catheter sited in the superior jugular venous bulb (fig 1). The blood was collected into preheparinised 1 ml plastic disposable syringes which were immediately capped. Each blood sample was then injected through a gas tight butyl rubber septum (Pierce and Warriner) into

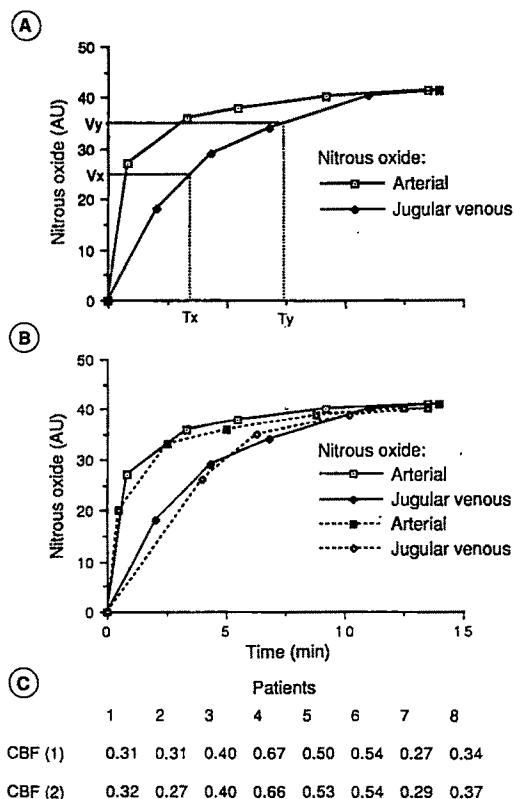


Figure 1(A) Arterial and jugular venous nitrous oxide saturation curves obtained by plotting the concentration of nitrous oxide in six paired, timed, blood samples withdrawn during the period of 10% nitrous oxide administration against time. V_x and V_y represent successive measured nitrous oxide concentrations at times T_x and T_y . The nitrous oxide concentration is plotted in arbitrary units (AU) as only the difference in concentration over time between the arterial and venous nitrous oxide saturation curves is required. (B) Duplicate arterial and jugular venous nitrous oxide saturation curves, obtained by taking 12 paired, timed, blood samples from the arterial and superior jugular catheters during the period of administration of 10% nitrous oxide. The solid lines represent the curves used to calculate one value for cerebral blood flow, CBF (1), and the dotted lines represent the curves used to calculate the second value, CBF (2). (C) Cerebral blood flow in ml/g/min obtained from performing duplicate measurements, CBF (1) and CBF (2), in eight patients (see methods).

3.5 ml glass vial (Pierce and Warriner) using a 25 gauge hypodermic needle. A second 25 gauge needle was inserted through the septum at the time of injection to avoid an increase in pressure within the bottle. Both needles were then withdrawn and the blood samples maintained at room temperature until the nitrous oxide concentration was measured.

Measurement of the concentration of nitrous oxide

To ensure that the nitrous oxide in the gaseous phase was in equilibrium with that in the blood sample a vortex was created in each sample by a 10 second agitation of the vial (Rotamixer, BDH).^{13 14} The gas above the blood sample was then sampled and its concentration assayed using infrared spectroscopy (ADC, M 715).^{15 16}

The coefficient of variation of the microassay technique was measured by performing six determinations of nitrous oxide concentration on 0.2 ml samples of heparinised blood tonometered at 37°C with three mixtures of nitrous oxide (5%, 10%, and 15%) and oxygen. The coefficient of variation of the technique ranged from 1.4% to 3.4%.

Calculation of cerebral blood flow

The arterial and cerebral venous nitrous oxide saturation curves were plotted from the concentrations of nitrous oxide in the six paired, timed, blood samples (fig 1). The areas under each curve were calculated using a computer programme and the equation:

$$\text{Area}_c = \sum \frac{(T_x - T_y)(V_x + V_y)}{2} \quad \text{Equation (8)}$$

Where Area_c is the area under the curve and V_x and V_y represent successive measured nitrous oxide concentrations at times T_x and T_y .

The numerator in the Kety Schmidt equation (6) was obtained by multiplying the blood brain partition coefficient for nitrous oxide (1.06)⁸ by the cerebral venous oxide concentration at equilibrium (fig 1).

The denominator in equation (6) was derived by subtracting the area under the venous curve from the area under the arterial curve. Cerebral blood flow in ml/g/min was thus calculated.

Reproducibility of cerebral blood flow measurement

In eight subjects the reproducibility of the measurement of cerebral blood flow was determined by taking 12 timed, paired, blood samples from the arterial and superior jugular catheters during the period of administration of nitrous oxide (fig 1). This enabled two separate values for cerebral blood flow to be calculated for each subject.¹⁷ Each measured value of cerebral blood flow was assumed to be the 'true' value plus error where the errors were assumed to have a normal distribution with variance sigma squared. The estimate of error was then calculated as:

$$\sigma^2 = \sum \frac{(x_1 - x_2)^2}{2n} \quad \text{Equation (9)}$$

Cerebral metabolism

At the end of the period of nitrous oxide administration, a blood sample (0.5 ml) was withdrawn from both the arterial catheter and the superior jugular venous bulb for analysis of blood gases and oxygen content. Blood gas analysis (pH, arterial carbon dioxide tension (PaCO_2), arterial oxygen tension (PaO_2), and base excess) was performed using a Radiometer blood gas analyser (Corning 1312). The arterial oxygen saturation (SaO_2) and haemoglobin concentration (Hb) were measured at the bedside by a Co-Oximeter (Corning 2500) and arterial oxygen content calculated according to the formula¹⁸:

$$\text{Oxygen content} = \text{Hb} \times \text{SaO}_2 \times 1.39 + (0.023 \times \text{PaO}_2) \quad \text{Equation (10)}$$

Results

JUGULAR VENOUS CANNULATION

Cannulation of the superior jugular venous bulb was attempted in 78 children and was successful in 72 (age range 2 weeks–16 years, median 2 years, weight 2.4–58 kg, median 13.3 kg). In six children cannulation was not successful (age range 6 weeks–6 years, median 4 months, weight range 2.4 kg–20 kg, median 5.37 kg); two were under 3 kg and another child was later found to have anomalous venous anatomy. In 68 cases the procedure was entirely uncomplicated. Puncture of the carotid artery occurred in four children but bleeding was easily controlled with local pressure.

The jugular venous bulb cannulae remained in situ for a median of 2 days, range 1–8 days. There were no clinical problems related to the cannulae. Of 47 catheter tips submitted for microbiological cultures, 40 showed no evidence of bacterial contamination and seven showed a scanty growth of skin commensal organisms.

Duration of nitrous oxide administration

To be able to calculate cerebral blood flow it is important to ensure that the duration of administration of nitrous oxide is sufficient to achieve equilibration of the nitrous oxide between blood and brain (fig 1). The period required is dependent upon the rate of blood flow to the brain. Kety and Schmidt administered 10% nitrous oxide by inhalation for 10 minutes.⁷ In normal adult subjects this was found to be sufficient to ensure blood-brain equilibration,⁷ indicated by the concentration of nitrous oxide in the cerebral venous blood becoming equal to the concentration in arterial blood (fig 1A).

Figure 2 graphs the time to achieve blood brain equilibration for nitrous oxide versus the calculated cerebral blood flow for 331 measurements made in the present study. In only 87/331 (26%) measurements was equilibration achieved by 10 minutes. In 276/331 (83%) of the measurements however equilibration was achieved after 15 minutes of nitrous oxide administration. More than 15 minutes was required to reach equilibration when blood flows were very low, with 42 of these 55 cerebral blood flows being less than 0.30 ml/g/min.

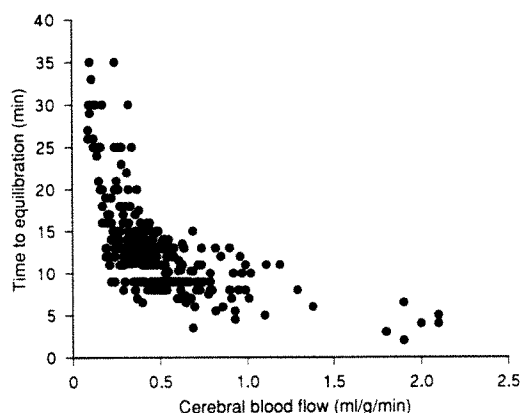


Figure 2 Time to blood-brain equilibration of nitrous oxide in relation to cerebral blood flow. Blood-brain nitrous oxide equilibration is defined as having been reached when the cerebral venous concentration of nitrous oxide is within 5% of the arterial concentration.

Reproducibility of measurements of cerebral blood flow

Figure 1B shows two arterial and venous saturation curves for nitrous oxide obtained from the same subject after the taking of duplicate, paired, blood samples during a period of administration of nitrous oxide (see methods). Figure 1C tabulates the paired values for cerebral blood flow obtained. There is close agreement between the two values for all eight subjects. The estimate of error (σ see equation (9) in methods) was 1.58% with a 95% confidence interval of 1.02% to 2.88%. Thus the measured values are likely to lie within $\pm 3\%$ of the putative 'true' value.

MEASUREMENTS OF CEREBRAL BLOOD FLOW AND METABOLISM

Three hundred and forty eight measurements of cerebral blood flow and metabolism were performed in 58 children. The median age was 2 years (age range 2 weeks–16 years) and the median weight 12.6 kg (range 2.4–58.0 kg). The median number of measurements performed in each child was 6 (range 1–23). It was possible to repeat measurements as frequently as every half hour if desired.

There was wide intersubject and intrasubject variability in cerebral blood flow results which ranged from 0.09–2.13 ml/g/min. Figure 3A shows the median value of cerebral blood flow plus the range for each of the 58 subjects in relation to their age. There was no systematic variation in values of cerebral blood flow with age.

There was similarly wide intersubject and intrasubject variability in the results for the cerebral metabolic rate for oxygen with a range of 0.03–5.79 $\mu\text{mol/g/min}$. Figure 3B graphs the median value of the cerebral metabolic rate and the range for each of the subjects in relation to their age.

In a normal subject, in whom cerebral blood flow and metabolism are closely coupled, the arterio-jugular venous oxygen difference remains constant. In a patient with acute encephalopathy this relationship between cerebral blood flow

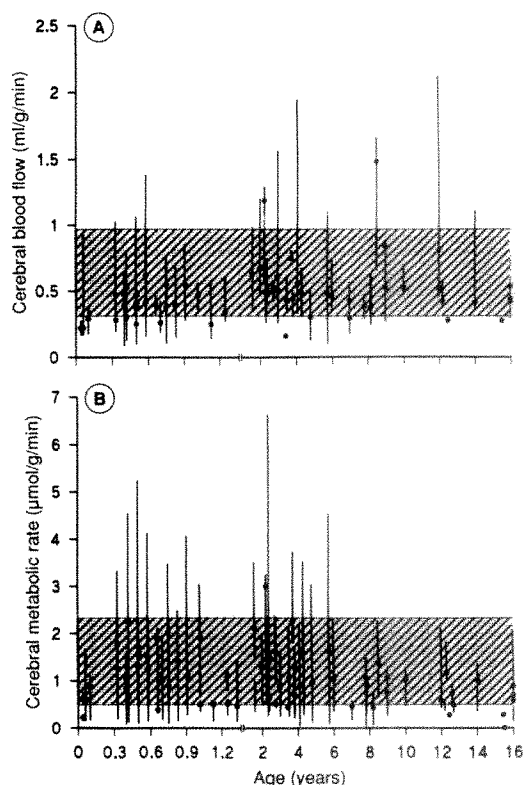


Figure 3 Cerebral blood flow (A) and cerebral metabolic rate for oxygen (B) for all 58 subjects in relation to age. The points represent the median values for each child, and the vertical lines indicate the range. The hatched area represents the limits of the range of cerebral blood flow (A) and cerebral metabolic rate (B) reported by Settergen *et al* in normal children.²⁰

and metabolism may be lost and abnormally high or low cerebral oxygen extraction may be found.¹⁹ An arterio-jugular venous oxygen concentration difference which is greater than normal indicates a cerebral blood flow that is low relative to cerebral metabolic rate while, conversely, an arterio-jugular venous oxygen difference that is lower than normal implies that cerebral blood flow is relatively excessive for the brain's metabolic demands.¹⁹

Figure 4 shows the relationship between cerebral blood flow and the arterio-jugular venous oxygen difference for all 348 measurements. The limits of the normal ranges for these parameters²⁰ are also shown. Using this model each result can be categorised into five broad groups (A, B, C, D, and E). In group A the cerebral blood flows and arterio-jugular venous oxygen concentration differences are normal, suggesting that there is a normal relationship between cerebral blood flow and metabolism. In groups B and C there is absolute or relative hypoperfusion; group B demonstrates increased cerebral oxygen extraction associated with low cerebral blood flow indicating hypoperfusion; group C demonstrates a high arterio-jugular venous oxygen extraction associated with normal or increased cerebral blood flow indicating a cerebral blood flow relatively insufficient for a high cerebral rate. In group D cerebral blood flow is within or above the normal range and oxygen extraction is decreased, indicating a cerebral blood flow that is excessive for meta-

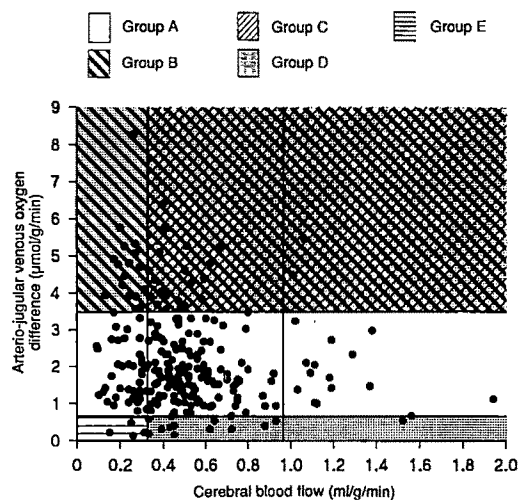


Figure 4 The relationship between cerebral blood flow and the arterio-jugular venous oxygen difference for all 348 measurements. The vertical lines represent the limits of the range of cerebral blood flow results reported in normal children by Settergen *et al*²⁰ and the horizontal lines represent the limits of the range of arterio-jugular oxygen differences.²⁰ The plain and variously hatched areas represent the five groups (A, B, C, D, E) into which an individual set of results can be classified.

bolic requirements. Finally, in group E, both cerebral blood flow and arterio-jugular venous oxygen differences results are below the normal range, indicating very low cerebral blood flow associated with low cerebral blood flow.

Discussion

This study has shown that the Kety Schmidt technique can be used in very sick children to perform serial, quantitative measurements of cerebral blood flow and metabolism on the intensive care unit. The Kety Schmidt technique has been used previously to measure cerebral blood flow and metabolism in very small numbers of children with acute encephalopathy,²¹⁻²⁴ but no other group has described the use of this technique to perform serial measurements in large numbers of very sick children.

The results of our study demonstrate that significant changes in cerebral blood flow and cerebral metabolic rate may occur over time within an individual subject (fig 3). Such wide variation during the course of the illness emphasises the need for a technique that allows repeated measurements of cerebral blood flow and metabolism to be performed; serial measurements also permit an assessment of the efficacy of therapeutic manoeuvres.

Other currently available methods of measurement cannot be used either at the bedside or to perform serial measurements. Thus, techniques that employ radioisotopes have limitations because of the hazards of repeated exposure to irradiation.²⁵ Positron emission tomography (PET) and single photon emission tomography (SPECT) have the additional disadvantage that the patient has to be transported to the scanner.^{25 26} Infrared spectroscopy may have potential as a method of performing continuous, focal measurements of

cerebral blood flow and metabolism in comatose children²⁷; however this technique is still being developed (J S Wyatt, personal communication).

The suitability of the Kety Schmidt technique for use in children has hitherto been a source of controversy. A major review of methods for measuring cerebral flow dismissed the technique as associated with major technical problems.²⁸ These difficulties have arisen from two sources: first, sampling blood from the superior bulb of the internal jugular vein and second, performing reproducible measurements of nitrous oxide concentration in small volumes of blood.

The original technique of direct puncture for sampling superior jugular bulb blood was technically difficult and associated with morbidity.⁹ However, percutaneous retrograde cannulation using the Seldinger¹⁰ technique is an easier procedure¹¹ and allows an indwelling catheter to remain in situ for the duration of intensive care. We have experienced no significant complications from this procedure and similar findings have recently been reported by Gale *et al*¹² and Goetting and Preston.²⁹

The original method for the measurement of the nitrous oxide concentration in blood, the Van Slyke manometric technique, required large volumes of blood and considerable expertise.^{15 23 30} Gas chromatographic analysis enables the volume of blood to be greatly reduced, but is technically demanding and labour intensive.³¹ The need for laboratory based equipment precludes immediate bedside measurement of cerebral blood flow. The use of infrared spectroscopy, however, overcomes these problems and enables the concentration of nitrous oxide to be measured rapidly and easily at the bedside in only 0.2 ml of blood.

Although other tracers, including krypton 85¹⁷ and tritiated water,³² have been used in the Kety Schmidt technique, low concentration nitrous oxide still has significant advantages, being safe, inexpensive, readily available, and stable. Moreover, the partition coefficient of nitrous oxide has been shown not to be altered by differing concentrations of lipid and water^{33 34} and thus is unlikely to change with age or if a subject develops cerebral oedema.

The duration of administration of nitrous oxide to ensure blood-brain equilibration has also been a source of controversy.^{35 36} It is clear both theoretically and from our results, that the period required is dependent upon the cerebral blood flow.^{35 36} In the light of our data (fig 2) we now administer nitrous oxide for 15 minutes. If the cerebral venous concentration of nitrous oxide is found not to be equal to the arterial concentration at the end of the measurement period, the venous curve is extrapolated^{35 36} to within 5% of the arterial value using a best fit monoexponential curve defined by least squares and a longer period of administration is used for subsequent measurements.

A major advantage of the Kety Schmidt technique is that normal ranges for cerebral blood flow and metabolic rate in children have been published by Kennedy and Sokoloff³⁷ and Settergen *et al*.^{20 31} However, although the arterio-jugular venous oxygen concentration differences reported by both groups are the

same (mean $2.17 \mu\text{mol/ml}$) there are significant differences in cerebral blood flow (mean 1.06 and 0.65 ml/g/min respectively) and cerebral metabolic rates (mean 2.30 and $1.35 \mu\text{mol/g/min}$ respectively) between the two groups. The values reported by Settergren *et al* are similar to the results for cerebral blood flow and cerebral metabolic rate in normal adult subjects quoted by other authors obtained using the Kety Schmidt technique^{7 38 39} and xenon 133 .¹⁹ Moreover, the nine children reported by Kennedy and Sokoloff were unsedated and restrained while femoral arterial and direct superior jugular venous bulb punctures were performed.³⁷ Thirty five other children were entered into the study but became so uncooperative that measurements could not be completed. The results were thus obtained from highly stressed children which may explain the high cerebral metabolic rates and consequent high cerebral blood flows. Settergren *et al* studied 70 children during general anaesthesia before elective surgery.²⁰ Anaesthesia was maintained with 50% nitrous oxide. A recent review has concluded that the effects of nitrous oxide anaesthesia on cerebral blood flow and metabolism in man are likely to be minimal.⁴⁰ We therefore concluded that results reported by Settergren *et al*²⁰ were more likely to represent cerebral blood flow and cerebral metabolism in normal unstressed children than those of Kennedy and Sokoloff³⁷ and these were used as our normal reference range.

Figure 4 illustrates how results for cerebral blood flow and arterio-jugular oxygen difference, available at the bedside, might be interpreted and aid clinical management. Thus, a child whose results fall within both normal ranges (group A) may not require treatment to alter cerebral blood flow or metabolism, unless intracranial pressure is significantly raised. If reduction of intracranial pressure is attempted by reducing cerebral blood flow then cerebral metabolic rate may need to be reduced in parallel. In contrast, a child with a cerebral blood flow which is relatively low for cerebral metabolic demands (groups B and C) is at risk of sustaining cerebral ischaemic injury and further lowering of cerebral blood flow would be inappropriate. Treatment might indeed aim to increase cerebral blood flow or lower cerebral metabolic rate. A child with relative hyperaemia (group D) would require no treatment unless intracranial pressure was raised, in which case reduction of cerebral blood flow might be appropriate.

At present the Kety Schmidt method is a research technique that will increase understanding of the pathophysiology of acute childhood encephalopathy. However, our success is using this method to perform frequent, serial measurements in relatively large numbers of children receiving intensive care, and the straightforward way in which the results can be interpreted, suggest that the technique may have potential in the future for the clinical monitoring of individual children and the evaluation of therapeutic interventions.

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Levamisole for steroid dependent nephrotic syndrome

They're always there, aren't they? I often see them as ward visitors so that they don't spend their lives waiting in outpatients. There's usually one, or two, at the end of each ward round. They need their height and blood pressure checking and steroid dosage adjusting. Some get cyclophosphamide but not with any great enthusiasm on my part (inwardly at least). Some have even been known to opt for 'alternative' therapies, receiving whatever is deemed good for 'kidney disease'. I don't mind that; it's when the alternative therapist starts to interfere with the steroid dose that I begin to lose my cool just a little. *They*, of course, have steroid responsive, frequently relapsing nephrotic syndrome.

There is evidence of deficient T cell function in this condition and therefore some rationale for using an immunostimulant drug such as levamisole, although the mode of action of this drug is unknown. A multicentre, randomised, placebo controlled, double blind trial done under the auspices of the British Association for Paediatric Nephrology has recently been reported (*Lancet* 1991; 337: 1555-7). Sixty one children completed the trial. All had steroid responsive, frequently relapsing nephrotic syndrome and had relapsed on maintenance treatment with prednisolone at a dose of at least 0.5 mg/kg body weight on alternate days. Remission was induced with prednisolone before starting levamisole (2.5 mg/kg to a maximum of 150 mg on alternate days) or placebo. The prednisolone was tailed off over eight weeks but the levamisole or placebo continued for 16 weeks.

At the end of 16 weeks 13% of the placebo group and 45% of those given levamisole had not relapsed ($p=0.008$). Most (10 of 14) of the levamisole treated patients in remission at the end of the trial, however, relapsed within the next three months. No serious toxicity was recorded.

It seems that levamisole offers some advantage as long as it is being taken. How long can we afford to give it for? Could we avoid steroid toxicity by alternating periods on steroid and on levamisole? Far more questions than answers come to mind. Judicious use in selected cases seems justified. It's certainly not a miracle cure.

ARCHIVIST

Sleep related upper airway obstruction in a cohort with Down's syndrome

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Abstract

The prevalence of sleep related upper airway obstruction (UAO) was studied in a cohort of 34 children with Down's syndrome from a geographically defined area. Thirty two (94%) of the children, ranging in age between 0.1 and 4.9 years (median 1.4), underwent full clinical assessment for UAO including parental questionnaires and overnight tape recordings of chest wall movements and arterial oxygen saturation (SaO_2). Compared with controls, children with Down's syndrome had (a) an increased incidence of stridor and chest wall recession during sleep, (b) an increased frequency of a pattern on inspiration indicating increased upper airway resistance, (c) a reduced baseline oxygen saturation (having excluded recordings on four children with potential for right to left intracardiac shunting), and (d) an increased number of episodes with $\text{SaO}_2 \leq 90\%$ despite continued chest wall movements.

At their initial assessment seven children (22%) had evidence of UAO. The 18 youngest children (≤ 1.7 years) underwent repeated recordings and clinical assessment until they had all reached 2 years of age. A further three were found to have developed UAO.

Sleep related UAO is a common problem in children with Down's syndrome, occurring in 10 of 32 (31%) of this population based sample.

Previous reports have shown that individuals with Down's syndrome are subject to upper airway obstruction (UAO).¹⁻⁴ Features of the anatomy of the upper airway are thought to predispose to this complication,² which when severe may lead to pulmonary hypertension and heart failure.⁵⁻⁷ In any child, UAO may be associated with poor growth, sleep disturbance, day time lethargy, chronic upper respiratory problems, and poor developmental progress.⁸ If present in a child with Down's syndrome, these may add to the total load of handicap suffered.⁹ As UAO may either increase in severity during, or only be present in, sleep, the patient suspected of suffering this disorder must be investigated while asleep.

The present study aims to determine the prevalence of UAO in a population of children with Down's syndrome in a well defined geographical area by using questionnaires and overnight multichannel physiological recordings. The subsequent clinical assessment and outcome are also described.

Subjects

The study consisted of three parts: (i) a case-controlled study of signs of UAO obtained by questionnaires administered to parents, (ii) a case-controlled blinded analysis of overnight tape recordings of arterial oxygen saturation (SaO_2) and breathing movements, and (iii) a clinical assessment for the presence of UAO which included the questionnaire, a clinical examination, and open assessment of the overnight tape recordings. This clinical assessment was also performed at the time of repeated recordings on the younger children until they had reached 2 years of age.

The study was approved by the local hospital ethics committee, and all parents of the controls and children with Down's syndrome gave informed consent.

CHILDREN WITH DOWN'S SYNDROME

All children up to 5 years of age with Down's syndrome from a well defined geographical area (Oxford Area Health Authority) are enrolled in a programme which offers support, clinical assessment, and coordination of services. Thirty two (94%) of the 34 children with Down's syndrome in this cohort were recruited to the study; two sets of parents declined. There were 20 boys and 12 girls, whose ages ranged from 0.1 to 4.9 years (median 1.4).

One subject (case 30) had undergone adenoidectomy for recurrent otitis media and one subject (case 14) had severe UAO in the neonatal period, as observed by Mugliston and Mitchell,¹⁰ but this had subsequently resolved. No other subject had undergone investigation or treatment for UAO, tonsillectomy, or adenoidectomy for any reason.

Twelve children (38%) were known to have congenital heart disease: five had ventricular septal defects, two had atrioventricular septal defects, three had complex structural defects, and one each had a secundum atrial septal defect and a patent arterial duct. Two of the 12 had undergone palliative surgery. Because cardiac function could have affected the respiratory measurements, a paediatric cardiologist, blind to the study findings, reviewed the case notes of the 12 children. At the time of the recordings, four children had a defect which might have resulted in baseline arterial hypoxaemia ($\text{SaO}_2 < 95\%$) (cases 1, 9, 15, and 22) and five children were considered to be tachypnoeic (cases 1, 2, 9, 15, and 22).

CONTROLS

Two sets of healthy infants and children with-

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out Down's syndrome were used as controls. For the questionnaire, 26 controls of similar age to the children with Down's syndrome were selected randomly; they ranged in age from 0.1 to 5.6 years (median 2.0) and there were 15 boys and 11 girls. For the overnight recordings, 32 different controls were selected randomly and matched individually to the subjects' ages; their ages ranged from 0.1 to 5.7 years (median 1.0) and there were 16 boys and 16 girls.

Methods

QUESTIONNAIRE

A structured interview was used to question parents about the presence of six clinical signs during sleep which from previous experience were known to be associated with UAO.⁴ These were inspiratory stridor (snoring), chest wall recession, sudden awakenings with a startle or gasp, restlessness, breathing through the mouth, and excessive sweating. The significance of differences in the incidence of these signs between children with Down's syndrome and controls was tested by Wilcoxon rank sum or χ^2 tests.

RECORDINGS

Twelve hour overnight tape recordings were performed on each child with Down's syndrome and each control (at the time of the above interviews for the subjects). Recordings included the following signals: (1) SaO_2 from a pulse oximeter (Nellcor N-100, with software identical to N-200) modified to provide beat-to-beat measurements. (2) The photoplethysmographic pulse waveforms from which SaO_2 was derived; these were used to identify and exclude SaO_2 measurements associated with movement artefact. (3) Chest wall movements from respiratory inductance plethysmography (Studley Data Systems) using a purpose made vest over the chest wall (P K Morgan) and from an abdominal volume expansion capsule (Graseby Dynamics). (4) End tidal carbon dioxide concentration, sampling from just below one nostril via a catheter leading to an infrared analyser (Engstrom Eliza). This last signal was collected for clinical assessment only (see below). The full recording technique has been described in detail elsewhere.¹¹ Recordings on both the children with Down's syndrome and the controls were performed in their homes, except for that on the youngest subject, who had remained in hospital after birth.

Tape recordings were printed out, using an ink jet chart recorder (Siemens 34T), at 3.2 mm/second. Measurements from the recordings were performed manually by two workers without knowledge of the source of the data and working to a protocol established for earlier studies.^{4,12} Breathing patterns were classified as being either regular or non-regular: a regular breathing pattern was signified by periods lasting at least one minute in which breathing movements were steady in rate and amplitude. All other periods of breathing movements, including those interrupted by body movements, frequent sighs or apnoeic pauses were classified as non-regular breathing.

Blind analysis of the recordings included an examination for:

(a) The presence of the pattern on the chest wall movement record indicating increased inspiratory resistance (false negative results may be obtained if tachypnoea is present and the five cases with congenital heart disease resulting in this pattern of breathing were, therefore, excluded from this analysis).

(b) Baseline SaO_2 , measured at the end inspiratory peak of five successive breaths in the centre of each period of regular pattern breathing, in an area separated by at least 10 seconds from disturbance of the chest wall movement by sigh or apnoeic pause. The mean of these measurements was calculated.

(c) Episodes of desaturation in which SaO_2 fell to $\leq 90\%$, the duration of each being measured. Apnoeic pauses were identified where there was a cessation of chest wall movement with a duration of ≥ 4 seconds. Episodes of desaturation were discounted if they showed a temporal relationship with such pauses: that is, where the beginnings of a pause and of a subsequent desaturation $\leq 90\%$ were separated by 2–12 seconds. This excluded the episodic desaturation that has been demonstrated to follow frequently and normally apnoeic pauses in healthy infants.¹³ The remaining episodic desaturations, that is, those associated with continued chest wall movements, were regarded as probably resulting from UAO. The durations of these episodes were summed in each breathing pattern separately, and expressed as durations per hour of artefact free signal. They were separated because SaO_2 instability has been demonstrated to be determined by breathing pattern, being reduced in regular pattern breathing.¹³

The significance of the differences for baseline SaO_2 , episodic hypoxaemia, and for the presence of increased inspiratory resistance between the children with Down's syndrome and controls was tested by the Wilcoxon matched pairs signed rank test or McNemar's test. One tailed tests were used throughout.

CLINICAL ASSESSMENT

All children with Down's syndrome underwent a clinical assessment which included the questionnaire described above, physical examination both awake and asleep, and an open examination of the overnight tape recordings of SaO_2 , breathing movements, and expired carbon dioxide concentration.^{4,11,12} A decision was made on the presence and extent of UAO and appropriate action was initiated, investigation and treatment being carried out at the Royal Brompton Hospital or local hospitals. If UAO was considered severe, further investigations might have been indicated (for example, cine barium swallow) before immediate referral was made for assessment in the ear, nose, and throat department. If the UAO was not considered to be severe further recordings were recommended in order to evaluate developmental changes of the impact of respiratory tract infection. The controls were not assessed in this way.

To assess changes with increasing age,

repeated recordings were performed on children who were <20 months of age at recruitment (cases 1 to 18). These recordings were made at target ages of 8, 14, and 24 months.

Results

QUESTIONNAIRE

This showed that the 32 children with Down's syndrome had a median of one clinical sign of UAO reported by their parents (range 0–5) and the controls had a median of 0 signs (range 0–3); this difference was significant ($p<0.01$, Wilcoxon). Ten children with Down's syndrome (31%) had three or more signs compared with one of 26 (4%) of the controls.

Looking at the six signs individually, only two appeared at a significantly higher frequency in the cases compared with the controls; these were inspiratory stridor (15/32 *v* 2/26, $p<0.001$, χ^2) and chest wall recession (11/32 *v* 0/26, $p<0.001$, χ^2). Sudden waking was not observed by parents of either group of children, while restlessness (15/32 *v* 9/26), breathing through the mouth (8/32 *v* 3/26), and excessive sweating (5/32 *v* 4/26) showed no significant difference between children with Down's syndrome and controls.

RECORDINGS

Increased inspiratory resistance

Eleven of the 27 children included in this analysis (41%) were found to have this pattern, compared with 1/32 (3%) controls ($p<0.005$, McNemar).

Baseline oxygen saturation

In the recordings of four children with Down's syndrome (cases 1, 2, 13, and 25), regular pattern breathing was not detected and it was therefore impossible to measure baseline SaO_2 by this method. For the remaining 28 children with Down's syndrome the baseline SaO_2 ranged from 73.5 to 100% (median 96.9) and for the controls from 98.3% to 100% (median 99.9%) ($p<0.0001$, Wilcoxon). Twenty children with Down's syndrome (71%) showed values below the lowest observed in the controls and two children had baseline $\text{SaO}_2<90\%$.

Excluding the results from children with Down's syndrome with a potential for right to left intracardiac shunting (cases 1, 9, 15, and 22, one of whom had no regular breathing pattern), baseline SaO_2 ranged between 87.9% and 100% (median 97.1), significantly different from the controls ($p<0.0001$, Wilcoxon). Of the 25 children with Down's syndrome, without relevant heart disease, and showing regular breathing, 17 (68%) showed values below the lowest observed in the controls.

Episodic desaturation to 90% or below

Two children with Down's syndrome (see below) had baseline $\text{SaO}_2<90\%$, which masked episodic desaturation, and their recordings were excluded from this analysis. For the remaining 30 children with Down's syndrome, desatura-

tions for the complete recordings ranged from 0 to 174.3 seconds/hour (s/h) (median 3.6) compared with 0 to 2.6 s/h (median 0) for the controls ($p<0.0001$, Wilcoxon).

For non-regular breathing pattern alone, the frequency of episodic desaturation ranged from 0 to 219.1 s/h (median 3.45) for the children with Down's syndrome and from 0 to 4.9 s/h (median 0) for the controls ($p<0.0001$, Wilcoxon). The frequency of episodic desaturation in regular breathing pattern alone for the 26 children with Down's syndrome ranged from 0 to 140.7 s/h (median 1.4) but for the controls only one score was greater than 0 (range 0 to 1.3) ($p<0.0001$, Wilcoxon).

CLINICAL ASSESSMENT FOR UAO

The first assessment indicated UAO in seven of the 32 children with Down's syndrome (cases 11, 12, 14, 18, 21, 23, and 29). The median age of these seven children was 1.6 years (range 0.7–4.2). At different ages, the proportion of children with Down's syndrome who demonstrated UAO was as follows: 1/11 (9%) in the first year of life, 4/11 (36%) in the second and third years, and 2/10 (20%) in the fourth and fifth years.

The results from these seven children were compared with those from the children with Down's syndrome ($n=25$) who had no, or only mild, evidence of UAO. The median number of clinical signs in the children with UAO was three compared with one. Two of the seven had a parental report of chest wall recession and six had inspiratory stridor, and one subject was reported as having no clinical signs (case 14). The seven children, none of whom had a cardiac defect considered to cause baseline hypoxaemia, had a lower median baseline SaO_2 (95.5 *v* 97.4%). In addition, six of the seven had values below the lowest observed baseline SaO_2 in the healthy controls. Compared with the children with Down's syndrome without UAO, the seven with UAO had more episodic desaturations in both non-regular breathing (median 24.6 *v* 2.4 s/h) and regular breathing (9.0 *v* 0.5 s/h).

A second clinical assessment was performed in 18 children with Down's syndrome, and a third in eight of these children. Three additional children (cases 8, 13, and 15) showed UAO at a follow up assessment, having not shown this on their previous recordings. All showed this after infancy (at ages 25, 24, and 18 months respectively). The number of clinical signs these children reported had increased from the number reported at their first recording (from 1, 1, and 3, to 4, 3, and 4 respectively); all showed inspiratory stridor and chest wall recession.

Seven children, followed later by a further three, were thus identified as having UAO (31% of the original cohort). All 10 were offered further investigation, but only eight sets of parents wished to proceed. Three patients underwent repeated clinical assessment and demonstrated no need for immediate intervention, two patients showed apparently spontaneous resolution, and three (9% of the cohort) underwent adenotonsillectomy at 30, 30, and

50 months of age. Six of the 10 children stayed in the programme and their full histories until their fifth birthdays are known. Two of the 10 children with UAO (cases 11 and 14) had moved from the area and were followed up by telephone at around 5 years of age; on contact both were found to need surgery to alleviate UAO (see histories below).

After the end of the formal part of the study two of the younger children, who were considered not to show UAO during the study period, have subsequently developed symptoms and, without formal clinical assessment, underwent adenotonsillectomy at 3 and 4 years of age respectively. Both children had a resultant diminution in their symptoms of UAO. One further child has also undergone adenotonsillectomy, at age 7 years, because of recurrent respiratory infections.

The cohort is now aged between 5 and 10 years. Overall, nine (28%) have undergone adenoidectomy or adenotonsillectomy: one before, and three during, the study period and a further five by the end of the recent follow up.

The case histories of six of the 10 children with UAO, highlighting certain aspects of management, are given below.

Case 8

This boy's assessments at 8 and 14 months of age had not demonstrated UAO. At 25 months a third assessment was positive and he underwent nasendoscopy, which showed modest adenoidal and tonsillar enlargement (the larynx and trachea were normal). At 30 months, because of an increasing frequency of respiratory tract infections, adenotonsillectomy was performed. An assessment after surgery showed no evidence of UAO and he became free of clinical signs.

Case 11

This boy showed clinical signs of obstruction, thought to be due to chronic catarrh, and was found to have appreciable UAO at his assessment at age 8 months. At 16 months of age UAO was less noticeable and subsequent assessment during a respiratory infection demonstrated that the UAO did not worsen. He moved home and when recontacted at 56 months of age, he was reported to have a high frequency of respiratory tract infections and a worsening of signs of UAO. A repeated assessment confirmed the presence of severe UAO and nasendoscopy showed adenoidal obstruction of the nasopharynx and oropharyngeal obstruction from palatine tonsils collapsing to the midline. Adenotonsillectomy was performed at age 60 months and was followed by disappearance of both snoring and nocturnal enuresis and a considerable reduction in both sleep disturbance and daytime somnolence. An assessment after surgery showed that UAO had almost completely resolved.

Case 12

This girl had signs of UAO at 1 year of age that were confirmed by a clinical assessment.

Nasendoscopy showed obstruction at the tongue base, with oropharyngeal shutdown resulting from tongue base and oropharyngeal incompetence. There was no adenotonsillar encroachment and her hypopharynx and larynx were normal. This obstruction would have been difficult to resolve. The treatment options were still under discussion when reassessment at the age of 24 months showed an appreciable lessening of UAO. This confirmed an improvement noted from clinical signs and no action was considered necessary.

Case 13

At 12 months of age this girl showed no evidence of UAO. At 24 months, however, clinical assessment showed severe obstruction that was confirmed by a history of increasing signs during her second year of life. At nasendoscopy it was only possible to examine the airway with the subject on her side because of the severity of the obstruction. The examination showed tonsillar shutdown and obstruction at the tip of the epiglottis, while the larynx and subglottis were normal. Before a routine adenotonsillectomy she suffered a choking and cyanotic episode at home, necessitating resuscitation by an ambulance crew. Surgery was performed urgently at 30 months of age. She was subsequently reported to be more alert, physically stronger, sleeping better, and had a post-operative growth spurt. At age 5 years she presented with sleep disturbance but clinical assessment showed that this was not due to UAO.

Case 14

This boy had severe UAO in the neonatal period but then recovered. An assessment at 15 months showed some UAO but his family reported no clinical signs. By 27 months of age he had developed signs and an assessment at that age showed severe obstruction. He underwent nasendoscopy which showed a significant adenoid pad, with 80% obstruction of the posterior choana, and large palatine tonsils. The epiglottis was posterior, with the aryepiglottic folds being drawn with inspiration into the laryngeal inlet. The vocal cords, subglottic region, and trachea were normal. As he still had few symptoms an expectant policy was adopted. He moved from the area, resulting in no further contact until age 5 years, when he continued to manifest severe symptoms of UAO with snoring, chest wall recession, and frequent awakenings from sleep. An assessment confirmed severe UAO and nasendoscopy showed a modest adenoidal pad obstructing 50% of the nasopharynx. The tonsils were non-obstructive and adenoidectomy alone was, therefore, performed. During the weeks after surgery he had no apparent relief from his signs and his treatment is currently being reviewed.

Case 15

This boy had congenital heart disease (secundum atrial and ventricular septal defects).

Assessments at age 2 and 12 months showed no evidence of UAO, but baseline Sao_2 had fallen over time and was thought to be due to his heart disease. At 18 months of age he had signs of UAO, but his recording showed tachypnoea (respiratory rate 51 breaths per minute in regular pattern breathing), making an assessment of inspiratory resistance difficult. A video recording during sleep showed stridor and chest wall recession. He underwent corrective cardiac surgery after which he had fewer clinical signs of UAO. He continued to thrive and develop well with only mild signs of UAO.

Discussion

The prevalence of UAO exacerbated by, or only present during, sleep in young children with Down's syndrome is high. Overall 10 children (31%) had obstruction identified during the study period: seven on their first recordings and three on repeated recordings. This complication was most prevalent in the second and third years of life. In children without Down's syndrome, sleep related UAO is related to the emergence of lymphoid hyperplasia, is uncommon in infancy, and most frequent between the ages of 1 and 3 years.¹⁴ Our experience with Down's syndrome reflects this observation and lymphoid hypertrophy did indeed prove to be a major contributing factor. Children clear of UAO in infancy would manifest the problem in early childhood and this sometimes resolved spontaneously at a later stage. Some of this variability in the degree of obstruction could reflect the effect of respiratory tract infections on the size of the lymphoid tissue. It should be noted, however, that adenoidal hypertrophy can occur during infancy and produce UAO (personal observations).

UAO sufficient to disturb sleep can interfere severely with day time performance. When associated with intermittent, or even baseline, hypoxaemia it may cause pulmonary hypertension.⁴⁻⁷ In addition, it may be life threatening, as in case 13. In children with congenital heart disease with left to right shunts it may hasten the development of pulmonary vascular hypertension.⁶ All professionals involved in the care of children with Down's syndrome should be alert to the high incidence of this complication.

Initial investigations, using the methodology outlined above, are non-invasive and minimally disruptive. They give a good assessment of the clinical and physiological severity of UAO, and help in deciding the need for further investigation and/or treatment. In particular they provide objective evidence of the effect of the obstruction on oxygenation. Expertise is required, however, to collect and interpret the physiological information. In the absence of these facilities examination of the child when asleep may show obstruction. Ideally the trunk should be exposed so that evidence of chest wall recession and tracheal tug can be identified; a video recording performed by parents on their child when asleep at home may be particularly helpful.

Examination of the upper airway is indicated

once there is evidence of UAO on history, video, or physiological recordings. To assess adenoidal size we recommend a radiograph of the postnasal space. In a patient with severe UAO we would consider performing a cine swallow before endoscopy, thus excluding the presence of a vascular ring. Examination of the upper respiratory tract requires a technique that can judge issues specific to Down's syndrome, such as the possible multiplicity of sites involved and the relationship between mechanical and functional obstruction, including the impact of marginally enlarged lymphoid tissue on a structurally narrowed airway. This is best accomplished by fiberoptic examination of the upper airway under light general anaesthetic with the child breathing spontaneously. Atropine alone is given for premedication as any form of sedation may precipitate acute worsening of the obstruction, or even respiratory arrest, in patients with sleep related UAO. The fiberoptic examination usually demonstrates the site and mechanism for obstruction, and if the presence of tonsils and adenoids is considered to be contributory, these can be removed under the same anaesthetic. A computed tomogram of the choanal area will be performed if there is evidence of narrowing in this area at endoscopy.

Specific problems arise where UAO coexists with congenital heart disease. Given the high rate of heart anomalies in Down's syndrome,¹⁵ there is a particular need to avoid alveolar hypoventilation, hypoxaemia, and the resulting pulmonary hypertension that may result from UAO. It can sometimes be difficult, however, to partition the causes for respiratory signs in patients who have both cardiac problems and UAO, as shown in case 15. In this child it was also interesting to notice a decrease in signs of UAO after cardiac surgery. Before surgery, left to right intracardiac shunting, an increased pulmonary blood flow, and decreased lung compliance may have resulted in compensatory increases in negative intrathoracic pressures, thereby exacerbating upper airway closure, a situation that was reversed after corrective surgery.

The site of UAO varied. The role of lymphoid tissue hyperplasia in causing, and therefore of adenotonsillectomy in alleviating, UAO is being increasingly recognised in children without Down's syndrome,¹⁶⁻¹⁸ and surgery was effective in a significant proportion of our cases. Although adenotonsillectomy may be effective for a proportion of children with Down's syndrome,^{2 4 19 20} patients should continue to be assessed in case this is not a complete or permanent solution. Alleviation at other sites is difficult and less effective, particularly if there is a disorder of muscle function in the tongue base and/or a disturbance in the size of the pharynx and hypopharynx, as suggested by Guilleminault and Stoohs²¹ and demonstrated in Down's syndrome by Brown *et al.*²²

The rate of adenotonsillectomy in this group of children with Down's syndrome was high with 28% known to have undergone either this procedure or adenoidectomy alone at some

point in their lives (9% during the study period). This compares with a rate in Britain of 0.8% of the total paediatric population for adenotonsillectomy.²³ Our children also appeared to need surgery earlier: the national peak period for adenotonsillectomy is 5 to 9 years of age²⁴ but six of our nine subjects underwent procedures well before their fifth birthday.

A small minority of children with Down's syndrome and life threatening UAO may require tracheostomy. In our limited experience this is successful in overcoming pulmonary hypertension but presents severe difficulties for the children's parents, particularly in relation to the high amount of mucosal secretions associated with Down's syndrome.⁴ Improvements are needed in surgical and non-surgical alternatives (for example, the use of nasopharyngeal tubes or nasal mask continuous positive airway pressure) if such an extreme, but sometimes essential, solution is to be avoided.

Sleep related UAO is a major and, in most cases, treatable cause of additional morbidity in children with Down's syndrome. Diagnosis is relatively straightforward, but there is a need for better treatment for the severe obstruction that may occur at the base of the tongue.

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New insights on gastro-oesophageal reflux in cystic fibrosis by longitudinal follow up

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Abstract

A higher frequency (25%) of gastro-oesophageal reflux (GOR) has been previously reported in patients over 5 years old with cystic fibrosis compared with controls without cystic fibrosis. It was believed that GOR was caused by the complications of cystic fibrosis. We looked for GOR in all 26 children younger than 60 months who had cystic fibrosis diagnosed. They had a classical genetic profile and the usual scattered clinical manifestations for age. GOR was confirmed in 21 (81%): 20 by abnormal pH tracings and in one on a clinical basis. After at least one month of adjusted cystic fibrosis treatment, antireflux treatment (cisapride) was given to 16 patients and variables of GOR improved dramatically. Weight gain was significant and recurrent cough and wheeze disappeared. One year later half of the patients still suffered from GOR. GOR is a major problem in the early life of those with cystic fibrosis and is not the consequence of either respiratory or gastrointestinal complications as it improves with age whereas cystic fibrosis becomes worse with age.

Bendig *et al* in 1982¹ and Scott *et al* in 1985² described a high frequency of gastro-oesophageal reflux (GOR) in older children and adults with cystic fibrosis compared with its frequency in the population in general.^{3,4} Vinocur *et al* found in 1985 a high frequency of GOR in children with cystic fibrosis under the age of 20 months.⁵ However in all these studies only those with cystic fibrosis and clinical evidence of GOR were investigated.

Prinsen and Thomas reported a study on infants with cystic fibrosis who had been receiving cisapride for clinically established GOR and who showed a higher weight gain than they would have expected solely from the relief of GOR. They concluded that cisapride, a gastrointestinal prokinetic stimulant known to

be effective in the treatment of GOR,⁷⁻⁹ had some anabolic action in patients with cystic fibrosis. Subsequent studies did not confirm this hypothesis.^{10,11} In these two studies no investigations were performed to ascertain the presence of GOR before the administration of cisapride.

GOR is known to cause gastrointestinal and respiratory complications in patients without cystic fibrosis.¹²⁻¹⁶ The aim of our study was to investigate whether GOR starts very early in life and gradually complicates the underlying cystic fibrosis disease or whether GOR is the consequence of other cystic fibrosis complications. Up to the present GOR has been considered to result from respiratory and abdominal involvement, as suggested in a recent review article.¹⁷ If this were true the frequency of GOR would increase with age. Also in the younger patients with cystic fibrosis there would be a propensity towards the same frequency as in the population in general. We decided to investigate the oesophagus of all babies and infants in whom cystic fibrosis was diagnosed. As far as we know investigations by pH tracings over about 20 hours have not been performed systematically in infants with cystic fibrosis before. In a first series of 10 children with cystic fibrosis who were less than 5 years old we found GOR in all of them.¹⁸ Surprised by these results we enlarged our series and arranged long term follow up of all cases. In 1989 we published the preliminary data of the pH tracings and reflux scintigraphies shortly after the diagnosis of cystic fibrosis in 23 patients younger than 5 years old.¹⁹ We now report in detail all available data including long term follow up in 26 patients.

Patients and methods

PATIENTS (TABLE 1)

As Scott *et al* had already studied older children with cystic fibrosis,² we considered only patients younger than 5 years when entering the study. From 1986 on all 26 consecutive babies and

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Table 1 Characteristics of the patients at first GOR examinations (13 boys, 13 girls)

Symptoms	Total (n=26)	Age		
		Neonates (≤4 weeks) (n=5)	6 Weeks-8 months (n=14)	18-60 Months (n=7)
Failure to thrive	11	2	7	2
Normal pancreatic function	1	0	1	0
Meconium ileus	5	1	3	1
Vomiting	7	2	3	2
Prolapsed rectum	2	0	0	2
Liver cirrhosis	1	0	0	1
Recurrent cough and wheeze	9	2	2	5
Respiratory infections	11	2	7	2

infants (13 boys and 13 girls) were investigated shortly after the diagnosis of cystic fibrosis, and all the data were collected. In this complete series five (19%) were younger than 4 weeks (considered as neonates), 14 (54%) were from 1 month to 8 months old, and seven (27%) from 18 to 60 months at the time of the first oesophageal pH investigation.

Respiratory and gastrointestinal symptoms of these patients were not uniform. There was no statistical difference in current symptoms between the three age related subgroups. Failure to thrive (11 patients) was considered to be present when the weight was below the third centile, or when it was more than 2 SDs lower than height. Eight patients suffered recurrent cough and wheeze without infection. Bronchial reactivity was not measured in them; however symptoms regressed moderately after salbutamol aerosol. One patient did not suffer from pancreatic insufficiency; this was demonstrated by echography of the pancreas and by analysis of the enzymes in the duodenal juice. He did not have diarrhoea or malabsorption despite not having supplements of pancreatic enzymes.

DIAGNOSIS OF CYSTIC FIBROSIS

In all patients the diagnosis of cystic fibrosis has been confirmed classically in the department of medical chemistry (Dr C Sevens) by pilocarpine iontophoresis on at least two occasions,²⁰ and on each occasion one separate test on each arm was performed simultaneously. At least 100 mg of sweat was collected on each arm and all chloride and sodium concentrations exceeded 60 mmol/l. The diagnosis was later also documented by genetic analysis in the department of human genetics (Drs I Liebaers, M Bonduelle, and W Lissens) with detection of deletions f508 and haplotypes.²¹⁻²³

DIAGNOSIS OF GOR

For this purpose we used prolonged pH monitoring performed in the paediatric clinic of gastroenterology (Dr Y Vandenplas), using a Memolog 2 a 200 (Novo Diagnostic Systems). The pH electrode (MI 506, Microelectrodes Inc) was introduced transnasally and its location in the middle third of the oesophagus was determined by fluoroscopy. The pH recordings were continuously measured for approximately 18-20 hours, starting in the afternoon and lasting throughout the night until the next day. Whenever the pH dropped below 4 it was considered that reflux was present.^{24, 25} All data were recorded on an Apple computer. A graphic tracing of the pH variations was drawn at the end of the recording period and the following variables were calculated: (1) Reflux index: the sum of the periods with a pH less than 4, expressed in % of the total investigation time. (2) The duration of the longest reflux episode in minutes. (3) The total number of reflux episodes, expressed per hour, for uniformity, as there were slight variations in the examination time for each patient. (4) The total number of reflux episodes lasting longer than five minutes also expressed per hour.

A pH tracing was considered as abnormal if the value of any one of these variables exceeded the mean +2 SDs as established in age matched healthy infants.²⁴ As the normal values for adults, as established by De Meester *et al*,²⁵ approached the ranges for children of 15 months and older we accepted these standards for our older children.

ANTIREFLUX TREATMENT

Cisapride (Prepulsid, Janssen Pharmaceutica) is a new potent gastrointestinal prokinetic drug that increases the tone of the lower oesophageal sphincter. The mechanism of action of the drug is believed to be enhanced release of acetylcholine from the myenteric plexus. It has been shown to be effective in the treatment of GOR, gastroparesis, and chronic constipation.⁷⁻⁹ We have used it previously in infants and children suffering from GOR and respiratory disease but without cystic fibrosis.^{26, 27}

Cisapride was available in syrup form at the concentration of 1 mg/ml and the usual dosage schedule was 0.2 mg/kg body weight four times a day 30 minutes before each meal. In some infants we needed to increase this dose to 0.3 mg/kg. Those with more than four meals received the fourth dose before the last evening meal.

The agreement of the hospital's ethical committee for this open treatment trial was obtained and the parents gave informed consent.

PATIENT OBSERVATION

All infants were first observed for some time (at least one month) under a classic cystic fibrosis treatment considered optimal: (1) Mucolytic aerosols and physical treatment for bronchial toilet, both at least once a day, irrespective of respiratory symptoms. (2) Hypercaloric and protein enriched diet, with sufficient fat, as balanced by the dietitian. (3) Pancreatic enzymes for all but the patient without pancreatic insufficiency. (4) Antibiotics only when needed. (5) No drugs that could enhance GOR, for example, theophylline.²⁸

Antireflux treatment was planned only in those patients with severe GOR whose previous treatment was not fully satisfactory. If within one month of cisapride treatment a favourable response was observed, that is, both an improved pH tracing and some decrease of the clinical complaints, it was planned to continue the treatment for at least one year.

STATISTICAL METHODS

The department of biostatistics at the faculty of medicine (Dr M P Derde) offered assistance in the statistical interpretation.

Each of the measured gastro-oesophageal variables of the pH tracings was evaluated by the number of SDs separating it from the expected mean value for age matched individuals.

Changes induced by cisapride treatment, either gastro-oesophageal variables or clinical variations, were evaluated with the paired non-

Table 2 GOR variables before treatment

Patient No	Sex	Age (months)	Reflux index (%)	(SD)*	Longest reflux (min)	(SD)*	Mean No refluxes/hour	(SD)*	Mean No refluxes >5 min/hour	(SD)*
1	M	0.5			Clinical diagnosis					
2	M	0.5	56	(14)	207	(23)	4.2	(8)	1.2	(12)
3	M	1.5	66	(46)	225	(40)	1.7	(4)	0.6	(9)
4	M	8	21	(5)	135	(15)	2.3	(4)	0.3	(2)
5	M	2	45	(19)	224	(58)	3.3	(5)	0.6	(6)
6	F	1.5	12	(7)	37	(6)	1.4	(3)	0.4	(6)
7	F	34	23	(11)	68	(8)	4.1	(5)	0.7	(11)
8	F	4	24	(9)	126	(32)	1.2	(1)	0.25	(2)
9	F	22	49	(24)	156	(21)	2.7	(3)	0.8	(14)
10	M	40	24	(11)	101	(13)	2.0	(2)	0.3	(4)
11†	F	8	0	(0)	1	(0)	0.6	(0)	0.0	(0)
12†	M	59	1	(0)	6	(0)	0.6	(0)	0.05	(0)
13	F	6	18	(5)	46	(5)	3.0	(4)	0.3	(2)
14	F	3	8	(2)	41	(7)	0.75	(0)	0.15	(0)
15	F	18	7	(2)	16	(1)	1.6	(1)	0.99	(6)
16	F	60	12	(5)	47	(5)	1.64	(1)	0.34	(5)
17†	M	6	2	(0)	2	(0)	1.0	(0)	0.0	(0)
18†	F	60	3	(0)	5	(0)	1.6	(1)	0.06	(0)
19	F	3	12	(4)	49	(11)	1.8	(2)	0.26	(2)
20	M	3	10	(3)	21	(4)	2.0	(3)	0.25	(2)
21†	M	4	0.1	(0)	3	(0)	0.48	(0)	0.0	(0)
22	M	0.8	52	(36)	170	(30)	2.0	(5)	0.59	(9)
23	F	0.8	32	(22)	243	(43)	2.1	(6)	0.6	(9)
24	M	3	16	(6)	44	(10)	1.8	(2)	0.38	(3)
25	M	1.5	11	(7)	38	(6)	1.34	(3)	0.24	(3)
26	F	0.5	13	(13)	21	(9)	1.08	(3)	0.41	(18)
Geometric mean‡			9		12		3		5	
Formulas			Ln (2.31 (0.78)) -1		Ln (2.57 (0.87)) -1		Ln (1.33 (0.52)) -1		Ln (1.84 (0.74)) -1	

*SDs separating the observed from the predicted values.

†Normal pH tracings.

‡Geometric mean of the SDs of the variables of the pH tracings.

Ln=natural logarithm.

parametric Wilcoxon test carried out two tailed. The non-parametric Spearman rank test was used to evaluate the severity of GOR in relation with age.

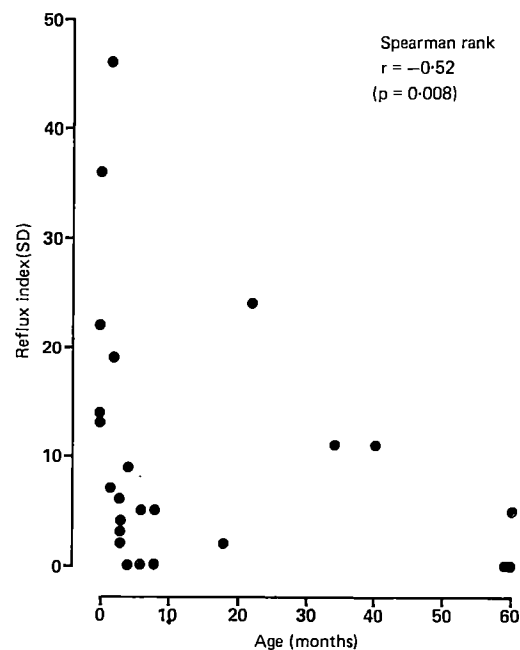
Results

Table 2 shows the results of the reflux variables in all patients before antireflux treatment was taken into consideration. In 20 patients there were severe refluxes with highly significant disturbed pH variables in most of them, especially the reflux index and the duration of the longest reflux, as shown by the very large number of SDs separating the observed from the predicted values (numbers in parentheses). Reflux was diagnosed in 21/26 patients (81%): in 20 by pH monitoring and in one (patient 1) on a clinical basis, because it was just before the diagnostic tools became available in our department (later on GOR was also confirmed by pH monitoring in this patient). In five infants pH tracings were normal, and perhaps because of the small number no difference in characteristics could be observed between those with reflux and those without, either clinically (not even for vomiting) or by genetic analysis (table 3). The infant without pancreatic insufficiency (patient 4) also had reflux.

The figure shows the relationship between the severity of the reflux index and the age at the first investigation. To avoid any bias and overestimation of the results those without reflux were also included and calculations were carried out two tailed. We observed a significant negative relation ($r = -0.5215$, $p = 0.008$). For the other pH monitoring variables similar significant negative relations with age were found: for the longest reflux $r = -0.5153$ ($p = 0.008$), for the number of refluxes per hour $r = -0.5239$

Table 3 Clinical and genetic comparison between infants with reflux and those without

Symptoms	With reflux (n=21)	Without reflux (n=5)
Failure to thrive	10	1
Normal pancreatic function	1	0
Meconium ileus	4	1
Vomiting	5	2
Prolapsed rectum	2	0
Liver cirrhosis	0	1
Recurrent cough and wheeze	8	1
Respiratory infections	8	3
Genetic investigation:		
Δ f508 homozygote	15	2
Δ f508 heterozygote	5	3
No Δ f508	1	0



Relationship between the severity of the reflux index expressed as the number of SDs separating the observed from the predicted values and the age in months at the first pH monitoring.

($p=0.007$), and for the number of refluxes longer than five minutes $r=-0.4127$ ($p=0.040$).

The cisapride trial was initially planned in 19/21 infants with reflux because of persistent symptoms with classical treatment: failure to thrive despite correct diet under pancreatic enzyme supplements ($n=10$), repeated vomiting ($n=5$), and signs of recurrent cough and wheeze ($n=8$). Finally the trial took place in only 16/21 with reflux: in patient 1 on a clinical basis, in 14 patients one month after the demonstration of GOR, and in patient 10 two years later. This boy was on the 75th centile and cisapride was not needed up to the age of 6 years when he developed recurrent cough and wheeze, without concomitant allergy, which did not respond to any classical treatment. The pH monitoring remained strongly abnormal and cisapride was eventually started.

Five of the 21 infants with reflux were not eligible for cisapride treatment: two babies (patients 25 and 26), respectively 6 and 2 weeks old at the diagnosis of cystic fibrosis and GOR, who needed further observation before the use of cisapride would be considered and three patients (patients 3, 6, and 15) in whom the parents refused the suggested treatment.

The five remaining patients (patients 11, 12, 17, 18, and 21) with normal pH tracings were also not eligible. Two of them (patients 12 and 21) nevertheless received cisapride because of clinical complaints and abnormal reflux scintigraphy.^{29 30} However because this technique is not sufficiently documented in cystic fibrosis they were not included in the treated group nor will their follow up be discussed.

EFFECT OF CISAPRIDE ON GOR (TABLE 4)

Of the 16 treated patients only 13 were available for pH monitoring one month after the onset of cisapride and a decrease of GOR was evident in 12/13. No improvement was found in patient 19 despite the dose being increased up to 0.3 mg/kg body weight. Despite disappointing results on pH monitoring we decided with the parents to continue cisapride.

EFFECT OF CISAPRIDE ON CLINICAL COURSE

Patient 2 suffered many unexplained respiratory

infections for which antibiotics and several aerosols were continuously given without success. He also showed severe growth retardation. Eventually a pH monitoring was arranged and after the confirmation of very severe GOR cisapride was introduced and all problems disappeared. This treatment was discontinued, with the authors' agreement, after three months of scrupulous treatment. He almost immediately developed clinically severe intractable asthma without underlying allergy and new pH monitoring again showed pronounced reflux. Both GOR and asthma vanished after the reintroduction of cisapride. This observation encouraged us to start the present study.

Part of the clinical evaluation one month after starting cisapride has been published previously.¹⁹ We can complete the evaluation and summarise as follows: (1) Eleven patients failed to thrive (including one without GOR and two with reflux without cisapride). All eight receiving cisapride showed an appreciable weight spurt within one month ($p=0.016$). The two patients followed up without cisapride treatment did not show a weight spurt. (2) Of the nine patients with recurrent cough and wheeze one had no GOR and he continued to wheeze after one month. The eight who had reflux received cisapride and in seven recurrent cough and wheeze disappeared immediately ($p=0.06$). After the initial weight spurt there was no further increase and most patients remained on the centile reached after the first month of cisapride treatment.

SIDE EFFECTS OF CISAPRIDE

Abdominal cramps occurred in patient 2 who received cisapride 0.3 mg/kg body weight four times a day for two weeks. These complaints disappeared after reducing the dose to 0.2 mg. No other side effects were observed. This was in agreement with previous studies.^{26 27}

LONG TERM FOLLOW UP OF pH TRACINGS (TABLE 5)

One year of follow up was completed for 23 patients. At that time pH monitoring was performed in 14/16 treated patients, after stopping cisapride for one week. It was also repeated

Table 4 Comparison of the SDs separating observed from predicted values before and during at least one month of cisapride treatment

Patient No	Reflux index (%)		Longest reflux (min)		Mean No refluxes/hour		Mean No refluxes >5 min/hour	
	Before	During	Before	During	Before	During	Before	During
2	14	2	23	1	8	7	12	0
5	19	2	58	1	5	1	6	1
7	11	1	8	1	5	1	11	1
8	9	1	32	1	1	1	2	0
9	24	1	21	4	3	1	14	0
10	11	0	13	0	2	0	4	0
13	5	0	5	0	4	0	2	0
16	5	3	5	0	1	2	5	5
19	4	5	11	10	2	1	2	3
20	3	0	4	0	3	0	2	0
22	36	3	30	4	5	1	9	1
23	22	2	43	6	6	1	9	2
24	6	1	10	3	2	2	3	1
Median	11	1	13	1	3	3	5	1
Range	36-3	5-0	58-4	10-0	8-1	7-1	14-2	5-0
p Value*	0.002		0.002		0.006		0.003	

*By two tailed Wilcoxon test.
All patients (except patient 19) improved considerably or even became normal ($SD<2$ for all variables).

Table 5 Comparison of the SDs separating observed from predicted values at the outset of the treatment with cisapride and one year later (after cisapride had been stopped for one week) in those with reflux

Patient No	Reflux index (%)		Longest reflux (min)		Mean No refluxes/hour		Mean No refluxes >5 min/hour	
	Outset	After one year	Outset	After one year	Outset	After one year	Outset	After one year
1	?	2	?	3	?	0	?	0
2	14	2	23	3	8	0	12	0
4	5	0	15	0	4	0	2	0
5	19	0	58	0	5	3	0	1
6	7	7	6	22	3	8	6	29
7	11	22	8	33	5	3	11	9
8	9	0	32	0	1	0	2	0
10	11	3	13	8	2	0	4	2
13	5	2	5	1	4	2	2	0
14	2	0	7	0	0	0	0	0
16	5	0	5	0	1	0	5	0
19	4	8	11	13	2	2	2	6
20	3	6	4	3	3	3	2	8
22	36	2	30	4	5	4	9	3
23	22	0	43	0	6	0	9	0
Median	8	2	12	2	3.5	1	3	0.5
Range	36-2	22-0	58-4	33-0	8-0	8-0	12-0	29-0
p Values	0.036		0.041		0.033		0.295	

pH monitoring was not justified in four of the five infants who did not have reflux, it could not be done in patient 3 who was lost to follow up, and was refused by the parents of patient 9; in patient 24 cisapride had not been taken for one year.

in patient 6 in whom the cisapride was refused. In five of 16 treated patients tracings became completely normal (patients 4, 8, 14, 16, and 23). The tracings of five with reflux who had been treated (patients 7, 10, 19, 20, and 22) as well as that of the infant who had not been treated (patient 6) remained severely disturbed. In four infants with reflux the tracings improved considerably with only one or two variables being slightly disturbed (patients 1, 2, 5, and 13). There is thus a significant tendency for GOR to decrease with time.

Repeat pH monitoring was not justified in four of five patients with initially normal tracings. Patient 11 was the first without GOR, despite severe uncontrollable and productive cough, and chronic consolidation of the right middle lobe due to a persistent *Staphylococcus aureus* infection. After a lobectomy performed at the age of 11 months and showing a purulent rupture of the right middle lobe bronchus, her respiratory condition improved dramatically and chest radiography showed slow normalisation. The many pH tracings performed before as well as after the lobectomy have always remained normal until now at the age of 3 years. Assuming that all five initially normal tracings remained normal and adding them to the 15 controlled tracings, the proportion of abnormal pH tracings falls from 21/26 (81%) to 10/20 (50%) and most of them are still younger than 5 years old.

Observations for longer than a one year follow up period on cisapride are scarce and not suitable for further analysis. The four patients with only mild GOR after one year of antireflux treatment evolved favourably without further need of cisapride. Three treated patients still suffering from severe GOR (patients 7, 10, and 20) could not do without cisapride after one year (and in patient 7 not after four years). This was because of an almost immediate recurrence of respiratory complaints at each attempt to stop cisapride. The tracing of patient 6, who was not treated with cisapride, remained severely disturbed for three years and then became normal

spontaneously despite repeated respiratory infections and obvious failure to thrive.

Discussion

Previous studies in patients with cystic fibrosis older than 5 years have shown a GOR frequency of 25%.² Our study performed systematically in all available patients less than 60 months old yielded a frequency of 81%. It is unlikely that this difference would be only coincidental. It suggests at least that the majority of newborns and infants with cystic fibrosis suffer from GOR. Comparing our own results in infants with cystic fibrosis with the findings in a paediatric population in general¹⁻⁴ it appears that GOR is much more common in cystic fibrosis. Contrasting this with our first hypothesis after the preliminary data on the first 10 consecutive young patients with cystic fibrosis,¹⁸ GOR is not systematically present in every baby with cystic fibrosis.

Another observation is that GOR occurred in infants with cystic fibrosis and babies whether respiratory symptoms were present or not. In patient 10 GOR clearly preceded the respiratory symptoms by many years. Furthermore patient 11 suffered severe respiratory complications even needing lobectomy, despite GOR never having been observed. In patient 6, despite her respiratory problems and her worsened hypotrophy, GOR disappeared without any specific antireflux treatment. These individual observations suggest that GOR is not the consequence of the respiratory problems, and in many patients respiratory manifestations decreased or disappeared with an efficient antireflux treatment while other treatments failed. GOR was also found in the baby without any pancreatic insufficiency, as proved clinically and biologically, which would suggest that it is not the consequence of any pancreatic abnormality. However more observations of pancreatic sufficient cystic fibrosis patients are needed to check whether our unique observation is not coincidental.

This series suggests two reasons that GOR has a tendency to decrease or disappear in many patients with age, explaining the decreased prevalence in the older patients as reported by other investigators²: (i) there is a significant negative correlation between the severity of GOR and age at the start of the study (figure) and (ii) repeat pH tracings in those with reflux after one year also shows a decreased GOR (table 5). Longitudinal studies on a very large series of cystic fibrosis patients are needed to establish whether early antireflux treatment can accelerate this. Compared with a group of patients with reflux disease without cystic fibrosis,³¹ GOR tends to disappear in cystic fibrosis at a later age and less frequently. From that point of view cystic fibrosis patients behave in a similar way to the population in general, only the magnitude of GOR and the rate of its persistence differ appreciably. The reason for the latter is unclear.

We were also surprised by the dramatic improvement, and often the return to normal, in a patient with previously severely disturbed pH tracing. This was especially true of the reflux index and the duration of the longest reflux immediately after cisapride was introduced. The exception was patient 19 who can be considered as a non-responder to cisapride; the decision to continue cisapride was arguable and her favourable development despite her GOR is probably not due to the cisapride. Until now no cystic fibrosis patient in our series needed Nissen fundoplication. Our results contradict the conclusion of Vinocur *et al* where Nissen fundoplication was needed in 33% of their patients.⁵ Nevertheless it should be stressed that before 1985 no valid medical antireflux treatment was available. Our results on patients with cystic fibrosis also contrast with our previous observation of children and infants with reflux pathology and respiratory disease not associated with cystic fibrosis. In these children the pH variables were much less disturbed before treatment but the response to cisapride, though significant, was less dramatic²⁷ and some needed Nissen fundoplication to achieve respiratory improvement.

The beneficial effects of cisapride observed initially by Prinsen and Thomas in some babies with cystic fibrosis could be due to the correct treatment of their GOR because of the great potential effect of the drug on this defect in those with cystic fibrosis.⁶ Cisapride has probably no effect at all in those with cystic fibrosis without GOR, which may explain the disappointing results of Smith *et al*¹⁰ and of Santamaria *et al*,¹¹ both of whom used cisapride without discrimination even in older patients with cystic fibrosis, some of whom probably did not suffer from GOR.

After the rapid relapse of respiratory complications in patient 2 when cisapride was stopped three months after first given, we decided on treatment for one year in all new patients in order to avoid too many repeated pH measurements. The safety of cisapride has already been established.^{7-9 27}

GOR even in the population in general can induce a variety of severe digestive and respira-

tory complications and be responsible for growth retardation.^{4 17 31} Patients with cystic fibrosis are susceptible to the same complications, starting in early life, but these can result both in irreversible lung damage and increased malnutrition. It is worth while mentioning that the occasional oesophagoscopy performed in three cystic fibrosis patients with reflux indices larger than 40% did not show oesophagitis, either on direct inspection or on the microscopic examination of the mucosal biopsy specimen and therefore we abandoned oesophagoscopy. The limited number of patients and the relatively short duration of the follow up of the present sample does not allow any objective interpretation of antireflux treatment on the overall course, except that all these patients benefited from the intensive and optimal cystic fibrosis treatment. It might be anticipated that appropriate antireflux treatment in cystic fibrosis with concomitant GOR can improve long term prognosis of cystic fibrosis. These issues are under further investigation and need many years of observation on a larger sample than the present one.

All these data seem to indicate that GOR in cystic fibrosis is caused neither by the respiratory nor the intestinal problems that have been the generally accepted explanations until now. This is because GOR can occur very early after birth and tends to decrease with age whereas respiratory problems in cystic fibrosis increase with time. We suggest that all cystic fibrosis babies and infants should benefit from systematic investigations for GOR, and also older cystic fibrosis patients if their treatment yields an unexpectedly bad response. Some of our older patients with reflux successfully responded to cisapride but are not reported here as they are not systematically investigated.

Further studies are warranted to answer the questions: Why does GOR occur much more frequently in babies and infants with cystic fibrosis than in the normal population? Why, despite the tendency of GOR to disappear in the population in general, does it remain in many patients with cystic fibrosis? To answer these questions the long term observation of those with cystic fibrosis who initially do not have GOR, though they seem to be less common, is at least as essential as the continuous observation of those with GOR. Indeed two different populations might exist: (i) infants who reflux early as described here in this paper and (ii) infants who reflux as a result of underlying respiratory or nutritional complications.

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Pregnancy in phenylketonuria: dietary treatment aimed at normalising maternal plasma phenylalanine concentration

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Abstract

The transport characteristics of the placenta, which favour higher phenylalanine concentrations in the fetus than in the mother, and regression data of head circumference at birth against phenylalanine concentration at conception in maternal phenylketonuria (PKU), suggest that treatment of maternal PKU should ideally aim to maintain plasma phenylalanine concentration within the normal range throughout pregnancy. A patient with classical PKU was treated from before conception by aiming to maintain plasma phenylalanine concentration within the range 50–150 $\mu\text{mol/l}$ and tyrosine within the range 60–90 $\mu\text{mol/l}$. The diet was supplemented with phenylalanine-free amino acids (100–180 g/day) and tyrosine (0–5 g/day). Plasma amino acid concentrations were monitored weekly by amino acid analyser. Dietary phenylalanine intake ranged from 6 mg/kg/day at conception to 30 mg/kg/day at delivery. Normal weight gain and fetal growth were maintained throughout the pregnancy. A normal baby was born at term with a head circumference of 35.5 cm; at 1 year of age no abnormality is detectable. These results show that with careful monitoring and compliance it is possible, and may be advisable, to maintain plasma phenylalanine concentration within the normal range in the management of PKU pregnancy.

developing fetal brain is likely to be at least as sensitive, if not more so, to damage by increased phenylalanine concentrations as that of the infant. These considerations would favour maintenance of maternal phenylalanine concentration at or below 50% of the recommended treatment range for infancy. This concept is taken further by regression data of phenylalanine concentration at conception in women with PKU against head circumference of offspring.⁶ These data have recently been extended to show that head circumference at birth falls by 0.46 cm for every 200 $\mu\text{mol/l}$ rise in phenylalanine concentration above normal.⁷ It has therefore been suggested that plasma phenylalanine concentration should be maintained in the normal range throughout pregnancy in a woman with PKU.⁷

We now report management and outcome of pregnancy in a woman with PKU using these principles. The limited sensitivity of the filter paper blood spot assay method⁸ led us to use the more precise method of automated amino acid analysis to monitor plasma amino acid concentrations, aiming for a therapeutic control range for phenylalanine of between 50–150 $\mu\text{mol/l}$ and for tyrosine of between 60–90 $\mu\text{mol/l}$ (that is, within the upper normal range). The rationale for control of tyrosine concentration was based on the remarkable inhibition of tyrosine transport into placental brush border membrane vesicles with increasing concentrations of phenylalanine.⁹

The dietary management of phenylketonuria (PKU) both in infancy and in pregnancy has generally been monitored by measurement of phenylalanine concentrations using filter paper blood spot specimens. The limited reliability of these measurements at low phenylalanine concentration and the importance of avoiding phenylalanine deficiency have led to generally accepted therapeutic ideal ranges for plasma phenylalanine concentration of between 200–400 $\mu\text{mol/l}$ in children under 8 years¹ and between 120–360 $\mu\text{mol/l}$ during pregnancy.² Preconceptional and gestational control of phenylalanine concentrations within these limits in maternal PKU generally results in offspring having an intelligence quotient (IQ) and developmental quotient within the normal range.³ As yet there are insufficient data to conclude that mean IQ is the same as that of the general population.

The concentration gradient across the human placenta results in the fetus being exposed to phenylalanine concentrations approximately twice those in maternal plasma.^{4,5} The

Case history

The patient was born in 1962 before the commencement of neonatal screening programmes for PKU in Australia. She first presented at the age of 2.5 years because of slow development and had a phenylalanine concentration of 1800 $\mu\text{mol/l}$. She was subsequently treated with a protein restricted, phenylalanine-free amino acid supplemented diet until the age of 9 years. Serial developmental assessments into teenage years placed her IQ in the low-normal range. Subsequent progress was uneventful until, at the age of 27 years, she planned pregnancy.

Dietary treatment was commenced 10 weeks before conception. The principles of the dietary regimen are summarised in the table. Phenylalanine-free amino acids, vitamins, and minerals were supplemented using a proprietary formulation (Maxamum XP, Scientific Hospital Supplies). An initial dose of 150 g/day was increased to 180 g/day at 24 weeks' gestation and subsequently decreased at 37 weeks to

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Principles of dietary management of maternal phenylketonuria aiming for normal plasma phenylalanine concentrations

	Before pregnancy	During pregnancy
Protein (as natural protein + amino acids)	<0.75 g/kg	<0.75 g/kg + 6 g
Phenylalanine	Initially 4–8 mg/kg,* adjust as indicated to maintain therapeutic range	Increase with advancing gestation to maintain therapeutic range
Tyrosine	Initially 160 mg/kg; adjust as indicated to maintain therapeutic range	Increase with advancing gestation to maintain therapeutic range
Calcium	800 mg	1100 mg first and second trimester, 1300 mg third trimester
Iron	12–16 mg	22–36 mg
Zinc	12–16 mg	16–21 mg
Folic acid (as total folate)	200 µg	400 µg
Macro and micro minerals and vitamins	Full range supplied from natural foods, protein substitutes, and supplements	
Essential fatty acids and cholesterol	From dietary fats and oils	
Energy	Individual assessment based on age, weight, appetite, activity	Add 850–1100 kJ to prepregnancy requirement
Weight gain		First 12 weeks: 1–2 kg Then 1–2 kg/month to term
Plasma phenylalanine	Monitor weekly, maintain 75–150 µmol/l for four weeks before ceasing contraception	Monitor weekly, maintain 75–150 µmol/l
Tyrosine	Monitor weekly, maintain 60–90 µmol/l for four weeks before ceasing contraception	Monitor weekly, maintain 60–90 µmol/l

*Depending on severity of PKU.
Intakes are given as daily requirements.^{10–12}

100 g/day as natural protein intake increased. The daily intake was divided into three equal portions and was taken with meals.

Changes in phenylalanine concentration in relation to dietary phenylalanine intake are shown in fig 1. Blood phenylalanine concentrations were monitored before conception and in the first four weeks after conception using filter paper blood spots and the bacterial inhibition assay; full amino acid chromatograms were obtained intermittently during this period. Subsequently, plasma phenylalanine and tyrosine

concentrations were monitored weekly by amino acid analyser (Biotronik LC 5000) because of concern over the precision of filter paper methods and the need to measure tyrosine concentration. All blood specimens were collected preprandially to simulate conditions under which the normal ranges were established. Blood was centrifuged and plasma separated immediately after collection. Plasma was then transported to reach our laboratory on the day of collection. After commencing treatment, the phenylalanine concentration rapidly fell to a little above the desired therapeutic range of 50–150 µmol/l. The patient's limited intelligence and her domicile in country Victoria, which restricted regular visits to the Royal Children's Hospital, made communication less than optimal on a number of occasions during the pregnancy. In mid-trimester plasma phenylalanine concentrations fell below the desired range several times, the lowest being 18 µmol/l at 15 weeks and 15 µmol/l at 22 weeks. These low concentrations may have been avoided through better communication. Plasma tyrosine concentrations (fig 2) were generally maintained close to or within the desired therapeutic range of 60–90 µmol/l. Tyrosine intake from natural protein, Maxamum XP, and additional tyrosine supplements is also shown in fig 2. The need for tyrosine supplementation additional to that provided by Maxamum XP and natural protein varied between 0 and 5 g/day; this was taken in three divided doses with Maxamum XP.

Maternal weight gain (fig 1) was satisfactory throughout the pregnancy, although there was some weight loss in the first trimester. Compliance with energy supplements in the form of

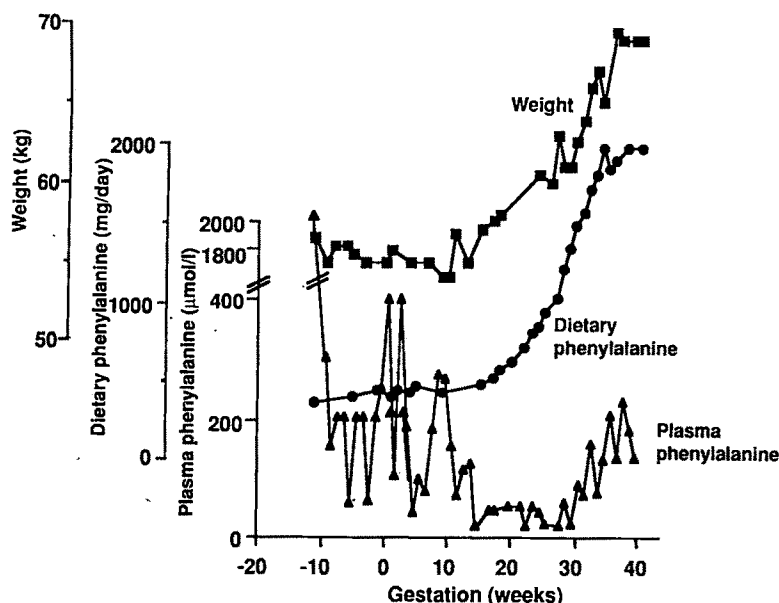


Figure 1 Dietary phenylalanine intake, plasma phenylalanine concentration, and maternal weight gain before and during pregnancy. Minimum phenylalanine concentration was 15 µmol/l at 22 weeks' gestation.

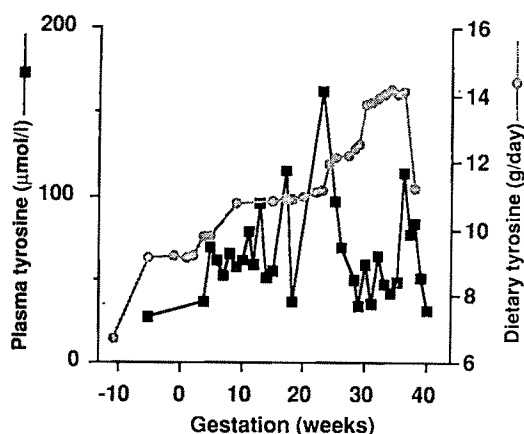


Figure 2 Tyrosine concentration in relation to intake before and during pregnancy.

low protein pastas and breads was poor at certain points during the pregnancy including the first trimester. Fetal growth was monitored by ultrasound examination at 18, 28, and 36 weeks of gestation. Despite suboptimal maternal energy intake and occasional sub-therapeutic phenylalanine concentrations, fetal growth was normal throughout the pregnancy. Ultrasound examinations revealed no evidence of malformation.

There were no obstetric complications throughout the pregnancy and the baby was born by normal delivery at 41 weeks' gestation. Birth weight was 3920 g (75th centile), length 51.0 cm (50–75th centile), and head circumference 35.5 cm (50–75th centile). The baby is quite normal to physical examination and now, at 12 months of age, has a Bayley developmental index (mental scale) of 106. Head circumference continues to lie on the 75th centile, weight on the 50th, and length on the 75th.

Discussion

The potentially disastrous effects of phenylalanine deprivation,¹³ the poor reliability of filter paper blood spot assay of low phenylalanine concentration,⁸ and the apparently good outcome of PKU treated by maintaining plasma phenylalanine concentration a little above normal,^{14, 15} have led to the great reluctance to maintain phenylalanine concentrations in children with PKU within the normal range. While mounting circumstantial evidence suggests that plasma phenylalanine concentrations should be better controlled during pregnancy than is necessary for treatment of childhood PKU,⁷ the exact optimal range is yet to be determined. We have demonstrated that the accuracy of amino acid analyser determinations of plasma phenylalanine and tyrosine concentration can result in very precise control of blood phenylalanine and tyrosine in PKU. The therapeutic range aimed for in this patient (phenylalanine 50–150 μmol/l, tyrosine 60–90 μmol/l) overlaps with that for normal pregnancy (phenylalanine 66–107 μmol/l, tyrosine 40–76 μmol/l, $n=7$, second trimester, personal communication, Dr E F Robertson).

No abnormality has been detected in the baby born to our patient. Head circumference measurements appear to be a sensitive indicator of outcome in maternal PKU^{6, 7} and on this measure the baby is normal. This conclusion is supported by a normal developmental assessment at 1 year of age. Nevertheless, complete evaluation of the strategy of maintaining normal phenylalanine concentration in maternal PKU will not be possible until a much larger number of cases similar to ours have been described and followed up long term.

At several points during the current pregnancy, compliance and communication difficulties resulted in phenylalanine concentrations falling outside the intended therapeutic range. Early in the pregnancy concentrations rose to 271 and 266 μmol/l at 9 and 10 weeks' gestation respectively. In a second pregnant PKU patient currently under treatment by the authors the phenylalanine concentration was well controlled before conception with a dietary phenylalanine intake of about 4 mg/kg/day, but the concentration rose to about 200 μmol/l in the middle of the first trimester. In both patients the first trimester increases most likely reflected difficulty in maintaining energy intake because of morning sickness of pregnancy. Our experience in conventional management of PKU pregnancy indicates that phenylalanine concentrations can be difficult to control in the first trimester. In the patient currently under treatment, control of the phenylalanine concentration within the desired range was obtained when an energy supplement in the form of glucose polymer (Polyjoule, Sharpe Laboratories, 100 g/day) was added to the regimen.

Very low phenylalanine concentrations were also documented on several occasions, despite which no symptoms of phenylalanine deficiency were noted in the mother and the baby continued to grow satisfactorily. The ability to concentrate phenylalanine across the placenta in favour of the fetus⁵ may protect the fetus from the effects of borderline maternal phenylalanine deficiency. Nevertheless, the potential risks of low phenylalanine concentration indicate the need for careful attention to increasing phenylalanine requirements, particularly during the second trimester. The narrow therapeutic range also requires accurate calculation of all dietary sources of phenylalanine including low phenylalanine bread, pasta, and biscuits and fruits and vegetables. Some of these foods are permitted without measurement in the diet of children with PKU on the basis that an average consumption provides a relatively constant intake of phenylalanine.

Tyrosine is a neurotransmitter precursor and low neurotransmitter concentrations have been suggested as one of the mechanisms by which damage may occur in PKU.¹⁶ An optimal range for plasma tyrosine concentration in pregnancy of a woman with PKU has not been established. The potential for even small rises in plasma phenylalanine concentration to inhibit placental tyrosine transport⁸ suggests that maintenance of tyrosine concentrations in the upper normal range may be ideal. Treatment with a tyrosine fortified formula such as Maxamum XP with

additional tyrosine supplements as required seems a satisfactory approach. The tyrosine concentration bore no consistent relationship to that of phenylalanine, presumably because the intake of each respective amino acid was adjusted independently in response to changes in blood concentrations. An unusually high tyrosine concentration (162 $\mu\text{mol/l}$) was recorded at 23 weeks. There was no clear explanation for this increase. However, it is likely that the concentration was even higher one to two hours postprandially on this occasion and the possibility that raised tyrosine concentrations may in themselves cause fetal damage should not be ignored.¹⁷ Excessive tyrosine supplementation should be avoided.

In summary, we have now documented for the first time implementation of a frequently discussed strategy of maintaining normal phenylalanine concentrations in maternal PKU. Early indications suggest a normal outcome, although long term follow up of this and subsequent cases will be needed to determine the advantages of this strategy as compared with those of more conventional treatment methods. Our experience coupled with solid theoretical background suggests that these further studies should be undertaken.

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Subdural fat effusion complicating parenteral nutrition

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Abstract

A preterm infant fed parenterally through a central venous catheter developed a subdural effusion containing fat emulsion. Subsequent postmortem examination failed to demonstrate any vascular abnormality that might have explained this rarely reported complication. Although retrograde flow of feeding solutions into cerebral veins seems a likely explanation, the exact mechanism remains uncertain.

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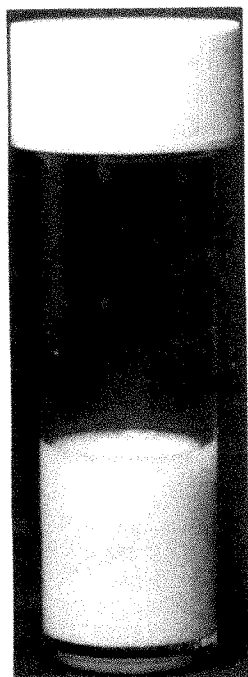


Figure 2 Milky white fluid aspirated by subdural tap with the biochemical composition of parenteral feeding fluids.

Technical problems may complicate parenteral nutrition. We report an unusual complication of a malpositioned central venous catheter, the aetiology of which remained obscure even after a full postmortem examination.

Case report

After the onset of premature labour at 26 weeks' gestation, a 925 g girl was delivered vaginally. She had an Apgar score of 6 at 1 minute and 9 at 5 minutes. Small bowel was noted to be prolapsing from a wound in the right iliac fossa that was caused by a penetrating abdominal injury to the mother two weeks earlier. The baby was ventilated from birth because of respiratory distress and transferred to the regional neonatal surgical unit. At laparotomy a small perforation of the ileum was resected and an end to end anastomosis performed. After surgery a percutaneous central venous catheter was advanced from an antecubital vein to the right atrium. The catheter was removed when full enteral feeding was achieved at the age of 13 days.

A patent ductus arteriosus and heart failure prevented weaning from the ventilator until surgical ligation at 16 days of age. Although respiratory function improved postoperatively, mechanical ventilation was again necessary after 48 hours because of a combination of infection and aspiration. Parenteral nutrition via a peripheral vein was reinstituted and continued over the next four weeks. During this time surgery was necessary to repair a left diaphragmatic hernia and postoperative recovery was complicated by peritonitis leading to a further laparotomy.

Gastro-oesophageal reflux and recurrent aspiration led to deterioration in respiratory function so that once again total parenteral nutrition was commenced. At 7 weeks of age a Vygon neonatal central venous feeding catheter was inserted percutaneously into the left posterior auricular vein. The catheter could be

advanced no more than 9 cm and radiography indicated that the tip was probably in the external jugular vein. However, blood could be aspirated back with ease and so the catheter was used for parenteral feeding over the next 33 days. At this time the child became drowsy, suffered a convulsion, and was noted to have a full fontanelle. Ultrasound examination showed fluid in the subdural space (fig 1), into which a 23G butterfly needle was introduced; 24 ml of milky white fluid were aspirated (fig 2).

CLINICAL PROGRESS

After aspiration of the subdural fluid the patient's neurological state returned to normal and the venous catheter was removed without any difficulty. Ultrasound examination showed no evidence of superior vena cava thrombosis and serial scans of the brain showed no re-accumulation of fluid or increase in ventricular size. Five weeks later death occurred from respiratory failure and a postmortem examination was performed.

INVESTIGATIONS

Microscopy of the aspirated subdural fluid showed no white or red blood cells and culture was sterile. Biochemical analysis revealed a glucose concentration of 44 $\mu\text{mol/l}$ and triglyceride content of 22.3 $\mu\text{mol/l}$ confirming that the fluid was largely composed of parenteral feeding solution and fat emulsion.

The postmortem examination demonstrated severe bronchopulmonary dysplasia. A detailed examination of the external jugular veins, sub-

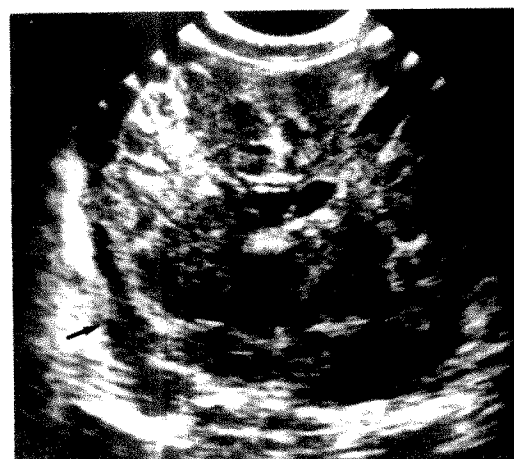


Figure 1 Coronal ultrasound scan of the brain showing a fluid filled space (arrow) between the brain and the skull from which lipid emulsion was aspirated.

clavian veins, superior vena cava, and intracerebral venous sinuses showed no evidence of thrombosis or anatomical abnormality. Cystic changes were evident in both occipital poles of the brain.

Discussion

Percutaneous central venous catheters provide reliable venous access in the newborn¹ and are widely used for delivering parenteral nutrition.² In contrast to the major complication of sepsis, serious mechanical catheter related problems are rarely encountered.³⁻⁴ Two previous cases of parenteral feeding solution accumulating in the subdural space have been described in preterm infants but neither case came to postmortem examination.⁵⁻⁶ In one of these patients the catheter tip was situated in the superior vena cava and swelling of the neck several hours after onset of neurological symptoms suggested a relationship between subdural effusion and superior vena cava thrombosis.⁵ In the second case report the catheter tip was left in the temporal vein with no clinical evidence of vessel occlusion, although the authors postulated a probable septic thrombosis.⁶

In the only case that has been subjected to a full postmortem examination our findings indicate that a subdural collection of intravenous feeding fluid may occur in the absence of venous thrombosis or apparent anatomical abnormality. This being the case, we would agree with suggestions that retrograde flow of parenteral nutrition infusion along the internal

jugular vein to the transverse sinus, sagittal sinus and, via a ruptured bridging vein into the subdural space, is the likely mechanism. Together with bronchopulmonary dysplasia, raised pulmonary vascular resistance might have been the cause of increased venous pressure giving rise to retrograde flow.

Subdural accumulation of intravenous feeding fluid appears to be a very rare complication of parenteral nutrition given via a misplaced central venous catheter. It would seem prudent whenever possible to site the tip of the catheter within the mid right atrium in an attempt to minimise the risk of venous thrombosis or retrograde flow. Acute onset of neurological symptoms in an infant with a central venous catheter should raise the possibility of a subdural effusion.

We would like to thank Dr S Variand for his help with the postmortem examination of this case.

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A national survey of nebuliser use

Helena J Childs, Carol A Dezateux

Abstract

Nebuliser drug delivery units were reused in 15% of paediatric wards participating in a national survey, while routine servicing and written information was provided by only half the wards issuing home nebulisers. Written information should be developed as a national resource, and further research on optimal cleaning practices is required.

Nebulisers are commonly used to treat children with severe asthma or cystic fibrosis in hospital and are increasingly prescribed for home treatment of very young children and those with chronic disease. While this may reduce the need for hospital admission, particularly of children with chronic conditions, it has been suggested that over-reliance on nebulised bronchodilators

and inadequate supervision and education may increase the risk of life threatening asthmatic episodes.¹ Nebuliser drug delivery units are manufactured for use by a single patient only, and though reuse may save money, potential hazards include bacterial contamination² and loss of efficiency of drug delivery. A recent King's Fund conference concluded that reuse of items manufactured for single patient use was undesirable and recommended development of guidelines governing reuse at district levels.³

This survey aimed to determine current cleaning and reuse practices and to obtain information on the advice and support given to parents issued with a home nebuliser in a nationally representative sample of paediatric wards in England. We also sought to establish whether guidelines governing reuse were available at district health authority level.

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Methods

Three district general hospitals selected at random from each of the 14 regional health authorities in England, and all regional, teaching, and specialist hospitals were included. Verbal informed consent to take part was obtained from the nurse in charge of each ward and a standard questionnaire administered at a subsequent prearranged time. All contact was by telephone (HJC).

Information was obtained for each ward on the following: (i) number of beds, (ii) number of children with asthma and cystic fibrosis admitted in the preceding calendar month; (iii) type of nebuliser drug delivery unit used, (iv) cleaning and reuse practices during an individual child's course of treatment and between children, and (v) and existence of a written ward policy for cleaning and reuse of drug delivery units. Staff responsible for issuing home nebulisers were identified, and details of advice on medical treatment, written material available for parents and children, as well as cleaning, operating, and servicing of home nebulisers obtained.

All district general managers in England were contacted by post to establish whether written guidelines on the cleaning and reuse of drug delivery units were available in their district.

Results

Two of the 77 wards contacted between February and August 1990 had closed and the nurse in charge of one ward refused to participate. Questionnaires were completed for 74 wards (96%) of which 43 were general paediatric, 29 medical paediatric, and two specialist respiratory wards. Most wards ($n=60$) had less than 30 beds. Information on admissions was available for 54 wards (73%); all had admitted children with asthma and 32 had also admitted children with cystic fibrosis in the calendar month preceding the questionnaire.

The System 22 or Hudson nebuliser drug delivery units were most frequently used (44 wards). The drug delivery unit was not changed in 56 wards (76%) during an individual child's course of treatment. Between drug doses, the drug delivery unit was not cleaned in 29 wards (39%), while in the remaining 45 the most frequent method of cleaning was washing with soap and water and drying. The drug delivery unit was kept at the child's bedside in 69 wards, and in 54 of these it was stored open to the atmosphere.

Although discarded in most wards when an individual child's course of treatment had been completed, the drug delivery unit was reused for another child in 11 wards (15%), 10 of which were admitting children with cystic fibrosis as well as asthma. Before reuse, the drug delivery unit was cleaned with soap and water and dried (six wards), or cleaned in sterilising solution (two wards), or sent to be resterilised (three wards). A ward policy on cleaning and reuse of nebuliser drug delivery units was available in only 17 wards.

All but two wards issued home nebulisers. In 52 (72%) of these, nursing and medical staff were jointly involved in educating parents on

issues such as drug dose, frequency of doses and when to seek medical advice. In 51 wards (71%), nursing staff alone were responsible for instructing parents on the operation of the home nebuliser and cleaning of the drug delivery unit. Written information for parents was provided in only 42 wards (58%), and for children in only three wards. Nebulisers were not recalled for servicing in 33 wards (46%) and only 23 (32%) met the British Thoracic Society recommendations of servicing twice a year.⁴

The regional, teaching, and specialist hospitals did not differ from the district general hospitals in any of the above practices.

Written replies were received from 177 of the 192 general managers contacted (92%); 110 district health authorities (62%) had no policy on cleaning and reuse of nebuliser drug delivery units. Information from 51 wards could be linked to that obtained from the relevant district health authority. Although general managers reported that a district policy was available for use in 22 of these wards, staff in only seven wards were aware of the existence of such a policy.

Discussion

Given the reported increase in hospital admissions for asthma in the UK and the rising number of nebulisers bought or supplied for use at home,⁵ the findings from this survey give cause for concern. Although manufactured specifically for single patient use, drug delivery units were reused in a number of paediatric wards. Almost all of these admitted children with cystic fibrosis, and reuse may increase the risk of bacterial cross infection to all children receiving nebulised therapy.^{2, 6} It is unclear to what extent a drug delivery unit may be reused, even for a single child, and to what extent its reuse may impair the efficiency of drug delivery. This could be of particular importance in the home when repeated use may occur for many months. Further research is needed on the optimal duration of use of the drug delivery unit.

It was of concern that there was no routine servicing of home nebulisers in almost half the wards, and servicing twice a year in only one third. District general managers need to be alerted to recently published guidelines on nebuliser maintenance.⁴ No policy on cleaning and reuse was available in more than half of district health authorities, and, even when available, nurses in charge of paediatric wards were frequently unaware of its existence.

There is a dearth of written information for parents and children issued with home nebulisers. Producing clear written information is a major undertaking and this should be developed as a national resource for parents as well as children, who, as they grow up, become increasingly responsible for their own treatment.

We would like to thank all of the nurses and district general managers who participated in this survey and Mark Whiting for commenting on questionnaire design. HJC was supported by the National Asthma Campaign and CAD by a Wellcome Research Training Fellowship in Clinical Epidemiology and the National Asthma Campaign.

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Familial infantile oesophageal achalasia

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Abstract

Oesophageal achalasia is uncommon in children and in its familial form it is a rarity. The presentation and management of two male siblings who presented with oesophageal achalasia as infants are reported. A high degree of consanguinity in the parents of the children existed, suggesting autosomal recessive transmission.

Oesophageal achalasia is a disease of unknown aetiology characterised by a functional obstruction of the lower oesophagus due to failure of relaxation of the lower oesophageal sphincter and altered motility of the body and distal oesophagus. It is an uncommon disease, usually presenting in adult life, and its occurrence in childhood is rare. Occasionally it occurs in a familial form. We report two male siblings who presented with oesophageal achalasia during infancy and who underwent corrective surgical treatment.

Case reports

The parents of the children were first cousins. Clinical examination and laboratory investigations excluded any syndromic type of achalasia in both cases.

CASE 1

A first born boy presented at 5 months of age with recurrent respiratory tract infection, abdominal distension, and failure to thrive. A barium swallow performed showed typical features of achalasia. At operation at the age of 10 months the child underwent a transabdominal modified Heller's anterior oesophagomyotomy of 8 cm length and Nissen fundoplication. The child is now well and thriving after three years of follow up.

CASE 2

The second and only other child in the family was also male and presented at 8 months of age with a history of respiratory tract infections,

regurgitation and vomiting, and failure to thrive since birth. Barium swallow was performed which again showed the features of well established achalasia (figure). Operation was performed at 10 months of age and again a transabdominal modified Heller's anterior oesophagomyotomy (8.5 cm long) with Nissen fundoplication was performed. The child made a good recovery postoperatively and is now thriving after six months of follow up.

Discussion

Achalasia of the oesophagus is uncommon with an incidence estimated at approximately one per 100 000 population per year.¹ In children achalasia is rare with only 2% of all cases presenting before the age of 6 years.²

A familial form of achalasia presenting in infant siblings was first described by Thibert *et al* in 1965.³ Before this in 1962 Tyce and Brough reported a family with multiple diseases inherited including mental retardation, oesophageal achalasia, speech disorder, and neurological diseases.⁴ Dayalan *et al* in 1971 reported the presentation of three siblings with achalasia during the first year of life.⁵ In the case they reported the parents of the affected children were closely consanguineous, the father being the maternal uncle of the mother; there were two boys and one girl.

Westley *et al* in 1975 proposed that infantile achalasia is inherited as an autosomal recessive disorder when describing its occurrence in an Apache Indian kindred.⁶ He postulated that the high degree of inbreeding allowed a rare recessive gene to be expressed in several members. The existence of consanguinity in the parents of the children in this report lends further weight to this argument. Although vertical transmission of oesophageal achalasia has been described, the lack of consistent vertical transmission is also thought to indicate a probable autosomal recessive gene disorder. Further support for autosomal recessive inheritance is the well documented occurrence of achalasia in association with other conditions having a similar mode of inheritance.



Barium swallow in case 2 showing achalasia.

We suggest that familial achalasia of the oesophagus may be transmitted as an autosomal recessive trait. We further suggest that parents of affected children be counselled regarding the risk of transmission to other offspring. A high index of suspicion is warranted in the follow up of siblings of index cases.

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Neonatal BCG

Randomised controlled trials have estimated the protective efficacy of BCG to be anything from zero to 80%. A recent study has put it at up to 97%. So we seem to be just three points short of a full house. Case-control studies may produce results in a much shorter time than randomised controlled trials, which means that not only do you have to wait a shorter time for the results but they may be more relevant to present circumstances when you get them.

The recent study referred to above is an excellent case-control study from Bangkok (Sayomporn Sirinavin and colleagues, *Pediatric Infectious Disease Journal* 1991;10:359-64). Altogether 130 cases of tuberculosis in children aged 3 months to 14 years were diagnosed in the two study hospitals between March 1987 and August 1988. These gave 75 cases and 207 controls suitable for analysis, the controls being matched for year of birth and district of residence. Those who had received neonatal BCG vaccination were compared with those who were unvaccinated against tuberculosis. Children who have been given BCG after the neonatal period were excluded from the analysis.

The overall protective efficacy of neonatal BCG was 83%. When the analysis was confined to laboratory confirmed cases and adjusted for socioeconomic status and household contact, the protective efficacy was 97%.

Neonatal BCG was shown to confer greater protection against more severe disease. In other words children who get tuberculosis despite vaccination are likely to have a less severe form. The protective efficacy against respiratory tuberculosis was only 64% but against superficial glandular tuberculosis it was 81% and against disseminated disease (meningitis, pericarditis, abdominal tuberculosis, and skeletal disease) 100%. Protection decreased from 96% in the first five years to 71% after six to 14 years. The degree of exposure to the disease is also important. With no household contact protection was 90% but when there was household contact it was only 50%.

The protection from neonatal BCG doesn't last forever. The World Health Organisation has apparently recommended revaccination at six years but the Thai workers suggest that 10 years would be more appropriate.

These results seem to provide ample justification for continuing to offer BCG vaccination in the neonatal period to at-risk groups in Britain and confirm its effectiveness for worldwide use.

ARCHIVIST

STATISTICS FROM THE INSIDE

1. Populations and samples

M J R Healy

This is the first of a series of notes on medical statistics. I hope to explain some of the basic ideas in a way which will be useful not only to those preparing papers for the journal but especially to those who read the papers that are published. I shall not attempt to go into details about the practical issues of analysing data as these are amply covered elsewhere; instead I shall try to convey the essence of the concepts which (like it or not) you are applying whenever you carry out a statistical analysis or interpret one in a published paper. Comments from readers would be welcome. Unfortunately, statistics is an odd subject in that the most difficult part comes first—the fundamental ideas are quite tricky to grasp, while the mechanics of bringing these ideas to bear are relatively simple. Accordingly, the first few of these notes are liable to be harder to come to terms with than the later ones.

The main objective of a statistical analysis consists in an attempt at *generalisation*. When you read a scientific paper which describes the effect of a new treatment on 20 patients, you are not usually interested in these 20 patients for their own sake; they are not your patients and they are in any case a thing of the past. Rather you carry out a statistical analysis or interpret one in a published paper. Comments from readers would be welcome. Unfortunately, statistics is an odd subject in that the most difficult part comes first—the fundamental ideas are quite tricky to grasp, while the mechanics of bringing these ideas to bear are relatively simple. Accordingly, the first few of these notes are liable to be harder to come to terms with than the later ones.

The underlying methodology of statistics—as of all science—consists in setting up a *model* of the situation at hand. Specifically, when confronted with a body of data relating to a number of patients, statistics considers a large collection of all the actual and potential patients to which you and others might wish to apply the results being analysed. This collection is known technically as a *population* (the word is a hangover from the origins of statistics in the 17th and 18th centuries). The objective of the statistical analysis will be to say something about this population. In order to do this, it is supposed that the cases reported constitute a *sample* from the population. To make generalisation possible, they must be a *representative* sample; in particular, they are almost always treated as if they were (or at least behaved like) a *random sample*.

Each member of the population will possess an *attribute* which is the subject of the study. This may be purely descriptive, such as ABO blood group, or yes/no, such as infected/not infected, or quantitative, such as family size or stature. A quantitative attribute may be a *discrete* count or a *continuous* measurement. This

attribute is known as the *variate* of the population (a population may have several variates, giving rise to *multivariate* problems). A statistical analysis is aimed at saying something about the different values of the variate which occur in the population (or populations) arising in the study. The phraseology for doing this is that of *probability*. Roughly speaking, the analysis aims at telling you how probable are the different values of the variate which occur in the population, that is, at describing the way in which the total probability of 1.0 is *distributed* over the possible variate values. Often (but not always) this is done by introducing a mathematical relationship between probability and value, using some form of *theoretical distribution*. The most familiar of these in practice, at least for continuous variates, is the so called *Normal* distribution (I write the name with a capital to stress that it is a technical term; its opposite is non-Normal, *not* abnormal). Discrete data in the form of counts can often be described by the *binomial* or *Poisson* distributions. Both of these closely resemble the Normal distribution when the counts are not too small.

The statistical model, then, assumes that the cases in a particular study are a random sample from a population. When you read an account of the study, you may also suppose that your own cases are another such sample from the *same* population. Knowledge about the population (based upon the sample in the paper) will then tell you something about how often different variate values might be expected to occur in your own experience—how many cases treated with a new drug might be expected to improve, for example. It is clearly a matter of judgment whether it is reasonable to consider the cases reported in the paper and your own cases as samples from the same population. To help with this, it is important for authors to report in detail the criteria and methods by which their cases were selected.

Statistics thus has the problem of finding ways of describing a population's variate values in a comprehensible way. First, we would wish to know whereabouts most of the values lie, their *location*. Various summary measures are possible, of which the most important are the *mean*, which is the straightforward average of the variate values, and the *median*, which is the middle value when all the values are arranged in ascending order. Almost all populations which occur in practice have values which cluster around a central value, with the probability of finding more remote values decreasing fairly rapidly. The central, most 'popular' value is called the *mode*.

Once we know the central location of the

variate values, the next question is their *variability*, how far away from the central value they commonly occur. To measure this, we might take each value, subtract the population mean to see how far the value deviates from it, and average all the *deviations* so formed. This does not work; the average is always zero, with the positive and negative deviations cancelling out. Instead, we can square each of the deviations and take the average of their squares. This average squared deviation is called the *variance* of the population. To make it more comprehensible, we can take its square root, and this gives the *standard deviation* (SD) which, as its name suggests, tells us a typical amount by which an observation might deviate away from the population mean.

If a mathematical form is being assumed for the shape of the distribution, the corresponding formula will contain one or more adjustable quantities which enable the formula to be adapted to the problem at hand. These are called the *parameters* of the distribution. If the values of the parameters are known, we can calculate from them the mean and standard deviation, and also the probability of observing different values of the variate—we could, in

fact, draw a diagram of the distribution, just as we could draw a circle if we knew its parameters, the position of the centre and the radius. The Normal distribution, as an example, has two parameters denoted by μ and σ . It so happens that these are equal to the mean and standard deviation of the distribution. The Normal distribution is *symmetric*, with equal deviations above and below the mean having equal probabilities; as a result the median and the mode are both equal to the mean. In a Normal distribution, some two thirds of all observations lie within 1 SD above or below the mean, and 95% lie within 2 SD above or below the mean.

The important thing to emphasise at this point is that what you *know*, as researcher or reader, are the variate values in the sample. What you would like to know is the description of the population, but about this there will inevitably be an element of *uncertainty*, and statements about the population will need to be phrased in the language of probability. There are two basic ways in which standard statistical methods are commonly used to generalise from the sample values in order to make probability statements about the population. These will be the subject of the next note in this series.

CHALLENGES

Paediatric care in the United States

Laurence Finberg

This is the third paper in a series showing the problems facing the medical services for children in different countries.

In writing this invited essay, I shall look at some of the problems facing the delivery of medical care to children of the US and not point to the glories of our successes of which there are many. On this side of the Atlantic we have pursued a system in which the general paediatric specialist (three years training in an accredited paediatric programme and successful passage of American Board of Pediatrics certifying examination) is both a primary care physician for children and a consultant to other specialists. To become a subspecialist additional training is required, now three years. Such persons are usually hospital based and care for patients within their specialised field, frequently giving primary care as well. This last varies from region to region and even from institution to institution. Some see this system as working well, others see it as a problem. We need more time to resolve the matter which I believe will happen as we address the more pressing problems of improving our medical care delivery system's economic basis. My experience as an educator and programme director leads me to believe that at least two years of training in paediatrics by paediatricians is needed for competency in the primary care of children and that at least three years of total (four would be better) postgraduate training is necessary for the average resident.

A few other thoughts should be reviewed before focusing on particular issues. Some of us believe health care is a 'right' akin to liberty and the pursuit of happiness. Others, for good reason, disagree and certainly our present legal system does not decree such a right. As a long time physician to children of the inner city I have believed all of my career that basic health care for *children* should be a mandated 'right' superseding even the wishes of parents. How *much* health care needs to be decided. I do not believe it will be hard to define 'basic' in this context.

So much has been said about the problems of delivery of health care in the US that any writing tends to be repetitive. Let us first list some of the facts generally agreed upon.

(1) Our costs are very high—nearly 12% of the gross national product and rising, far more than anyone else.

(2) Children have been getting proportionately less government monetary resource than the elderly, a situation which had been worsening until this year.

(3) Some of the outcome measures, for example, infant mortality, show the US lagging well behind other industrial nations, though this too has finally shown a spurt of improvement.

(4) One of the reasons for improvement, the availability for abortions for unwanted children, is under attack and we have seen retrogression in programmes for the poor where such programmes have been especially useful in lowering infant mortality. The antiabortion groups of course will say that mortality has been simply displaced in time, without that group having a parallel concern for the misery and hardships produced without these programmes.

(5) We profess a great unwillingness to ration medical care while at the same time actually rationing it by income rather than some other method.

(6) The private insurance system of payment and our tort laws have spurred a system where 'defensive medicine' and high malpractice premiums have increased the cost of care.

(7) The magnificent technologies we (and others) invent and produce have greatly advanced therapeutic medicine but not preventive medicine to our detriment. Some fortunate recipients of high tech care have benefited but other instances have only added to cost. In particular we can postpone dying long after useful life has ceased and have in so doing enormously raised costs.

(8) We abuse our treasured freedom by unwise personal conduct with respect to alcohol, drugs, tobacco, and promiscuity that add to our burden of illness without an economic penalty for these actions, another major cost item.

(9) Largely because the economic rewards for specialists, particularly those who perform procedures, are appreciably greater than for those who give 'primary care', our medical school graduates quite naturally compete for the more remunerative specialties which then have a high proportion of 'the best and brightest'.

I will now focus on a few of the problems of US health care as they relate to children: infant mortality, preventive services, and the disproportionate rewards for procedural services.

First a look at infant mortality. The prelude to birth, of course, is pregnancy. There is a clear positive association between appropriate prenatal care and good outcome in pregnancy. Many observers, missing the lack of a cause and effect relationship between these two, assume that simply more available access to prenatal care will solve the problem. I believe it will do little, because many (probably) of the women who do not get prenatal care do not *seek* it because they live in circumstances where health care for themselves or their fetus is simply not a high, or even moderate, priority. Some do not seek care because of ignorance. I therefore believe that the most important components of a programme to increase successful prenatal care

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requires measures to motivate and to inform the young women.

Of the two, motivation is the more important and the more difficult. One suggestion is to provide jobs for the economic underclass community so that there is hope for a better life. This of course requires political will and some sacrifice, probably through taxation, for the affluent. Simultaneously we should improve the education of the economically deprived so that they can at some point in the near future qualify for jobs requiring skills not now possessed in their community. Investment in these two areas will, I believe, ultimately pay off handsomely to the whole society. This suggestion goes outside of medicine to larger issues of the society. Medicine can ameliorate but not alone solve society's ills.

Ignorance about health matters can be reduced by introducing an understanding of the role of preventive measures and parenting at an early point in the school curriculum and reinforcing the information every year from about the age of 10 onwards. This last can be done easily and the paediatric community should be given a leadership role in devising the curriculum and perhaps even directly teaching some of it.

Preventive services must be administered to all children if we are to maximise our knowledge and improve children's health. I include here encouraging breast feeding, supervision of nutrition, plotting the points on the growth curve at appropriate and regular intervals, and administering immunisations to all except a few who may be medically vulnerable. Here we have failed to educate our physicians sufficiently in that minor illness is not a contraindication for immunisation. Much of the immunisation programme can be carried out without visits to a physician and we should return to that type of programme where suitable. Education about sexual behaviour and about harmful substances should also be a routine part of the school curriculum as a national necessity without

regard to the precepts of groups who would hide information and proscribe protective measures against disease and unwanted pregnancy.

Finally we find that our medical students, following their own reasonable self interest, do not, in sufficient numbers, choose careers that will best serve society's interest. In a free country we have only a few options. Like many before me I believe some form of nationalised system of medical care is needed, a system that will provide a comfortable economic niche for all physicians by redistributing the rewards toward 'cognitive' services and away from procedures. A redesign of fee structure will be needed rewarding (to a degree) length of training, difficulty of procedure, *and* the outcome performance of the physician, with a clear limit to annual reimbursement from the plan. These last remarks of course get beyond the field of paediatrics but are highly germane and, of course, very controversial.

I have not dealt with the problems of access to high technology and to the high cost of dying because these topics are now under debate and do not lend themselves to a solution that I can visualise. I do think that that new procedures should have a designated period when they are 'experimental' and not made widely available. Then each should be introduced and made available more generally after there is reason to believe it will prevent disease or sustain productive life. The *individual* decisions about the prolongation of dying I believe properly belong in the domain of physicians—not the courts with obligatory consultation with other physicians of experience.

The foregoing essay has provided a mixture of facts and highly personal opinion bearing on the solution to some of our problems. Some of these issues have also been reviewed in a single issue of the *American Journal of Diseases of Children*, May 1991; 145:489–580. Other views and suggestions are recorded there for the interested reader.

CURRENT TOPIC

Lyme disease in paediatrics

B Cryan, D J M Wright

The cluster of 39 children with a presumptive diagnosis of juvenile rheumatoid arthritis in Connecticut, around the town of Old Lyme, initiated the research which eventually led to the arthritis being named Lyme arthritis.¹ The association with a multisystem illness then caused the syndrome to be redefined as Lyme disease. Epidemiologically, an infectious aetiology appeared probable, with ticks as likely vectors for the disease. Clinically, a skin rash, erythema migrans, preceded the development of the arthritis. The skin rash had been first described in Scandinavia in 1913 and associated with tick bites.² Some patients presented with Bannwarth's syndrome, a meningopolyneuritis associated with tick bites, described in Europe as early as 1941.³ A possible causative organism, *Borrelia burgdorferi*, was isolated from a tick in 1982.⁴ This hypothesis was substantiated when the spirochaete was grown from blood, skin lesions, and cerebrospinal fluid (CSF) of patients with Lyme disease, and the disease was reproduced in rabbits, fulfilling Koch's postulates.⁵⁻⁶ Since then the disease has been recognised in many American states, Northern Europe, Russia, China, and Japan.⁷ It has also been reported in the southern hemisphere in Australia.⁷

Transmission

B burgdorferi is transmitted by the ticks of the genus ixodes. *Ixodes dammini* is most frequently implicated in the eastern USA. In the western USA and Japan *I pacificus* predominates. *I ricinus* acts as the vector in Europe with *I persulcatus* in Asiatic and European Russia.⁸⁻⁹ The nymphal ticks become infected by *B burgdorferi* while feeding on small mammals such as the white foot mouse, which act as reservoirs of the spirochaete. The natural hosts of mature ticks are large mammals such as deer. Humans are incidentally bitten when they enter a tick infected area, usually forest or scrub land.¹⁰ Children playing in such areas would be at particular risk of infection. The frequency of infection after a tick bite depends on a number of factors, such as the prevalence of *B burgdorferi* infection in the ticks, the duration of tick attachment, and the number of tick bites. In an English study of forestry workers, 25% had serological evidence of *B burgdorferi* exposure, and 5% symptoms attributable to Lyme disease.¹¹ These workers may have had multiple bites whereas positive Lyme serology was recorded in 20% of Austrian and 7% of Irish

populations who reported single bites.¹²⁻¹³ Another English study reported positive serology in 12% of a population comprising farmers, gamekeepers, and forestry workers.¹⁴

Epidemiology

Since 1982 the number of cases of Lyme disease in the USA has increased from 500 to over 4500 in 1988. The highest incidence is in children of less than 15 years and in adults of 25-44 years.¹⁵ Females were infected in 51% of cases. Data on file at the Charing Cross Lyme Disease Reference Laboratory records approximately 600 cases per year or 0.39 cases per 100 000 people. Most seropositivity is detected in middle aged patients, and the number of males is equal to that of females. In the eastern USA most cases occur in the summer months,¹⁰⁻¹⁵ which follows the period of maximal host seeking activity of nymphal ticks in May and June.¹⁶ In the western USA, cases are most common in spring.¹⁵ At Charing Cross there are two peaks, one in spring and one in autumn. Most Irish cases have come to medical attention in the autumn.

Clinical features

Typically, the clinical features of Lyme disease occur in three stages.¹⁷ There is considerable overlap between stages of the disease, and features of late Lyme disease may develop without any history of early disease. One of the 'unsolved mysteries' of Lyme disease is that there have been no outbreaks of arthritis reported since the initial 'cluster' in Connecticut.

The characteristic rash, erythema migrans, develops 2-30 days after the tick bite. This expanding lesion is centred on the insect bite and spreads outwards over a period of weeks. It is seen in up to 50% of patients and is occasionally due to multiple bites.¹⁸ Non-specific constitutional symptoms may occur at this stage: malaise, anorexia, lethargy, arthralgia, headache, roseola skin rash, abdominal pain, cough, and sore throat are common complaints. Patients, especially children, may be feverish.

The second stage of Lyme disease develops 1-4 months after infection. These patients tend to come to medical attention in the autumn or winter. Lymphocytosis cutis occurs in 1% of European cases but has not been reported in the USA. This lesion is a firm red to purple nodule or plaque. It develops on the ear lobe in children and on the nipple and areola in

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adults.¹⁸ Pathologically there is a dense dermal nodular lymphocytic infiltrate involving B and T lymphocytes. Infrequently, similar lymphocyte infiltrates, at the base of the brain in Lyme borreliosis, have been misdiagnosed in children as B-cell lymphomas.

Central nervous involvement is common. Lymphocytic meningitis, cerebellar signs, cranial polyneuropathy, and radiculopathy have been reported. The differentiation from Guillain-Barré syndrome may be difficult, but in neuroborreliosis the lymphocyte count is usually greater than 50 cells/mm³ and oligoclonal bands may be seen. Encephalitis, often clinically indistinguishable from herpes simplex encephalitis, may occur. Outside the UK one must consider other arthropod-borne encephalopathies in such cases. In an Austrian study of 21 children seropositive for Lyme disease, 17 had central nervous system involvement, three had arthritis, and one had skin symptoms.¹⁹ In this study and in a Swedish report aseptic meningitis and seventh nerve palsies were the commonest neurological features described.^{19 20} Pain in joints and soft tissues and rarely asymmetrical large joint arthritis may occur at this stage. These episodes are brief and recurrent.¹⁷ A self limiting myocarditis, which may necessitate the insertion of a transvenous pacemaker, infrequently presents during this phase of the illness. Bradycardia is not otherwise a feature of the disease. Iritis or panophthalmitis has also been reported, as has isolated inflammation of peripheral muscles.¹⁷

In the third stage, joint disease is most common. As many as 10% of patients may progress to a chronic erosive arthritis.¹ In an American study of Lyme arthritis in 43 children²¹ the mean age was 7.8 years and the male:female ratio 7:1. The knee was involved in 41 patients, the elbow in eight, the hip or ankle in four, and the wrist in two.²¹

At this stage in older patients demyelinating encephalopathy, polyneuritis, and memory impairment may become manifest.¹ Acrodermatitis chronica atrophicans is the characteristic skin rash of this phase of the disease. Initially this is a violaceous and often oedematous area of skin in plaques or nodules, which later atrophies. It resembles but is distinct from scleroderma.^{17 18} Acrodermatitis is unusual in childhood Lyme borreliosis but at least two cases have been described.²² Eosinophilic fasciitis is a rare complication.¹⁷

As many as 30% of patients do not demonstrate erythema migrans or other signs of early disease before presenting with late complications.²³ In European Lyme disease, joint manifestations are reported to be less common than in the USA. Conversely, in Europe nervous involvement tends to be more prominent.^{24 25} In North American Lyme disease, erythema migrans is more often multiple than in Europe. Recent reports suggest that these differences may be less extreme.^{13 26}

The isolation of *B burgdorferi* from the blood has raised the possibility of transplacental transfer of the organism. To date, borreliæ have been isolated from one stillbirth and one newborn infant but congenital abnormalities

resulting from Lyme disease during pregnancy have not been unequivocally demonstrated.²⁷ The abnormalities that have been recorded were associated with serological evidence of infection in retrospective studies.²⁸

Laboratory diagnosis

The laboratory diagnosis of Lyme disease is difficult. The organism has been grown from infected tissues such as skin and body fluids, including CSF.²⁹ Culture is an insensitive technique in most hands and not suitable for routine diagnostic use. Visualisation of the pathogen in infected tissue has similar limitations.³⁰ For these reasons serological techniques have been employed as routine diagnostic aids.

Indirect immunofluorescent assay (IFA) techniques were initially used to detect antibodies *B burgdorferi* but recently, as demand for tests has increased, enzyme linked immunosorbent (ELISA) methodologies have become popular. Such tests can be automated, allow objective test reporting, and are easier to standardise than IFA methods.³¹

Initial antibody responses are directed against the unsheathed flagellar proteins.³¹ A rise in IgM antibodies directed against a 41 kDa flagellar antigen can be detected in most patients two to four weeks after infection. This response peaks at six to eight weeks. Assays which detect IgM response to such proteins are very useful early in the disease. ELISAs which use purified flagellae or flagella enriched preparations of whole *B burgdorferi* as antigens have increased sensitivity in early disease.^{32 33} Later in the course of the illness antibodies directed against proteins in the outer surface membranes (OSP), such as the 34 kDa OSP B or the 31 kDa OSP A, are detected.³¹ As *B burgdorferi* shares many antigenic determinants with other bacteria, sera may contain antibodies which cross react in the IFA or ELISA assays described.^{31 32} False positive results can also occur in patients with connective tissue disorders.³⁴ Therefore further definition of the immune response by immunoblotting is a necessary confirmatory procedure if such tests provide positive results. Immunoblot patterns in children are similar to those of adults.³⁵ At the Charing Cross Lyme Disease reference laboratory 11% of the ELISA specimens that are weakly positive and a third of those that are strongly positive are confirmed by immunoblot. False negative results have also been reported: as many as one in three patients with erythema migrans are seronegative on initial testing,²³ and may become seropositive on further testing. Antibiotic treatment early in the illness may abrogate the antibody response to *B burgdorferi*.³⁶

A suitable test system would include a sensitive screening test, such as an ELISA which uses whole *B burgdorferi* or a flagella enriched preparation as the antigen. All positive results would then be checked by immunoblotting. Where clinically indicated, specimen testing would have to be repeated. In most instances serum would be a suitable specimen, but if neurological syndromes are being investigated CSF should also be examined. In one study nine

patients with neurological syndromes suggestive of Lyme disease had serum which was positive by ELISA, but only one had a CSF positive by ELISA and immunoblot and also evidence of intrathecal antibody production.¹³

In interpreting the laboratory results one must be aware that a proportion of the population will have serological evidence of previous exposure to *B burgdorferi* which may be unrelated to their current symptoms. Seropositivity rates of approximately 25% are detected in high risk populations such as forestry workers or orienteers.¹¹⁻³⁷ Clinical symptoms attributable to Lyme disease were detected in 5% of the forestry workers and 0.8% of the orienteers.

Modern advances in molecular genetics and the application of techniques such as the polymerase chain reaction (PCR) may resolve some of these diagnostic problems. A PCR assay using a highly conserved area of *B burgdorferi* chromosomal DNA was able to detect fewer than five copies of complementary DNA. The assay did not cross react with *B hermsi* or eukaryotic DNA.³⁸ The same authors expanded their primer range and were able to differentiate between *B burgdorferi* of European or American origin.³⁹ Using a PCR method, *B burgdorferi* DNA was detected in the urine of four of eight patients with clinical syndromes suggestive of Lyme disease.⁴⁰ If there is a high prevalence of *B burgdorferi* genetic material in the urine of infected patients, detection may simplify the laboratory diagnosis of Lyme borreliosis. By such techniques we may be able to detect these organisms in body tissues and further define the pathogenesis of Lyme disease. Classifying borrelia by PCR may provide valuable epidemiological information which would have especial relevance to vaccine development strategies.

Treatment

The aims of treatment in Lyme borreliosis are (a) to speed the resolution of the patients presenting illness and (b) to stop the progression to major long term sequelae.

It is probably best to avoid prophylactic antibiotics for people who have been bitten by ticks, as the likelihood of an individual developing Lyme disease is small and there is always a risk of an unexpected allergic reaction to antibiotics.⁴¹ Insect repellents to prevent the attachment of the tick are more practical. Nursing and medical staff attending patients with Lyme disease do not require prophylaxis as person to person transmission is unknown.

A particular problem of Lyme disease is that the clinical outcome cannot always be predicted from the sensitivity of the causative bacterium to antimicrobial agents in vitro. *B burgdorferi* is sensitive to a variety of common antibiotics, such as benzylpenicillin, erythromycin, tetracycline, amoxycillin, ceftriaxone, and cefotaxime. Antibiotics such as metronidazole, rifampicin, and sulphonamides have no role in the therapy of Lyme disease. The new quinolones and the aminoglycosides are likewise ineffective at clinical dosages.⁴²⁻⁴⁴

An oral agent is preferable in the treatment

of early Lyme disease. Erythema migrans and its associated symptoms resolved significantly earlier in patients given tetracycline or penicillin than in those treated with erythromycin.⁴⁵ None of 39 patients treated with tetracycline developed major late complications but 8% of the 40 patients given penicillin, and 14% of the 29 erythromycin treated patients did. All drugs were used in a dosage of 250 mg four times daily for 10 days. In a more recent study, no statistically significant differences were detected in the responses to tetracycline or penicillin therapy in erythema migrans. The tetracycline treated patients, however, developed fewer long term major complications, and fewer of them required further courses of antibiotic therapy.⁴⁶

Oral doses of tetracycline, 250 mg four times a day, produce peak serum concentrations four times the minimum inhibitor concentration (MIC), whereas phenoxymethylpenicillin in oral doses of 500 mg four times a day produces serum concentrations equal to the MIC.⁴⁷ Doxycycline in a dosage of 100 mg twice daily may be a convenient alternative. Amoxycillin combined with probenecid has also been used successfully to treat early Lyme disease. A recent study compared amoxycillin and probenecid (500 mg of each three times) to doxycycline (100 mg twice daily). All patients had early skin manifestations of Lyme disease and the duration of therapy was 21 days in each case.⁴⁸ In all patients the erythema migrans resolved and none developed major late sequelae. Symptoms after treatment such as fatigue, headache and arthralgia, developed in 15% of patients and persisted for up to three months. Such symptoms have been noted by other authors and resolve. They are twice as likely to occur in patients with disseminated early disease than in those with single lesions.⁴⁹

The duration of treatment depends on the severity of the illness: 10 days is thought to be adequate in mild cases with skin manifestations but 21 days may be more appropriate in cases of disseminated disease. Longer periods of treatment do not reduce the incidence of major or minor late sequelae.⁴⁹ In children less than 9 years old tetracyclines are contraindicated. In such cases amoxycillin and probenecid orally for 10 to 21 days are the drugs of choice. Erythromycin is a less effective alternative for penicillin sensitive children. In children older than 9 years, oral doxycycline is the most appropriate therapy. Amoxycillin with probenecid is an alternative.

The classical treatment for the neurological signs of Lyme disease was high dose parenteral penicillin.⁵⁰ In patients who manifest an uncomplicated Bell's palsy the outcome is usually favourable, and unless symptoms of meningitis or radiculitis are present oral administration is probably adequate. In a Swedish study of doxycycline treatment for neurological Lyme disease, doxycycline concentrations of 0.2 to 1 mg/l were obtained in the CSF during a regimen of 100 mg twice daily, all patients had a favourable outcome.⁵¹ On a treatment schedule of 200 mg twice daily, CSF concentrations of 0.6-1.9 mg/l were achieved. The MIC of *B burgdorferi* was exceeded in the CSF after the

first day of this dosage, but three to five days of treatment was needed to achieve comparable levels on the lower dosage regimen.⁵²

Treatment for patients with meningitis or radiculitis should be more aggressive. Parenteral penicillin in doses of 20 megaunits daily for 10 days has been used as standard treatment for neuroborreliosis. Results have been disappointing and the isolation of *B burgdorferi* from the CSF of a patient being treated with penicillin underlines the inability of penicillin to kill spirochaetes which may survive under sub-optimal conditions.⁵³ From the results of in vitro studies, third generation cephalosporins appear effective.⁴²⁻⁴⁴ Ceftriaxone has a half life of 8.5 hours.⁵⁴ In the absence of meningitis it crosses the blood-CSF barrier to give CSF concentrations 1.5% of those in serum. Two to four hours after an intravenous infusion of 2 g of ceftriaxone, CSF concentrations three to four times the MIC for *B burgdorferi* may be obtained.⁵⁵ It has been used successfully and proved superior to parenteral penicillin in late neuroborreliosis.⁵⁶

Though experience with ceftriaxone in Lyme meningitis or radiculitis is limited it appears to be a useful agent.⁵⁷⁻⁵⁸ An association has been demonstrated between the use of ceftriaxone and the development of biliary concretions. This antibiotic is as yet unlicensed in the UK.⁵⁹ As an alternative cefotaxime may be used and is equally effective.⁵⁸ The duration of treatment depends on the clinical response and usually varies between 21 and 30 days. In a patient treated for 10 days with parenteral ceftriaxone *B burgdorferi* was isolated from the CSF 7.5 months after treatment.⁵⁶ Recovery from meningitis is relatively rapid but radicular signs may persist for up to 24 months.⁴⁹

Lyme encephalopathy is probably best treated by parenteral ceftriaxone, or by benzylpenicillin as a less effective alternative.⁵⁶⁻⁶⁰ There is a case report of the successful use of cefotaxime in Lyme encephalitis.⁶¹

In patients with Lyme chronic synovitis, treatment failure rates of up to 50% have been reported, especially if erosive changes are present.⁶² Ceftriaxone is superior to penicillin, with therapeutic success rates of over 90%.⁵⁶⁻⁶⁰ Oral doxycycline or, alternatively amoxycillin with probenecid, have been used to treat these patients, with success rates of 72% and 61% respectively.⁶³

The use of corticosteroids in patients with chronic synovitis increases the risk of antibiotic failure and they are best avoided.⁵⁶ The development of chronic synovitis with a poor response to therapy has been associated with HLA DR4 and HLA DR2 alleles.⁶⁴

Jarisch-Herxheimer reactions are encountered in 14% of patients treated for early Lyme disease. They occur within 2-4 hours of starting treatment and are more common in severe disease.⁴⁵ Meptazinol unlike adrenocorticosteroids, has been shown to ameliorate such reactions in relapsing fever.⁶⁵ Meptazinol may be useful in cases of Lyme disease involving vital organs.

In conclusion, Lyme disease is a serious disorder with potential immediate and long

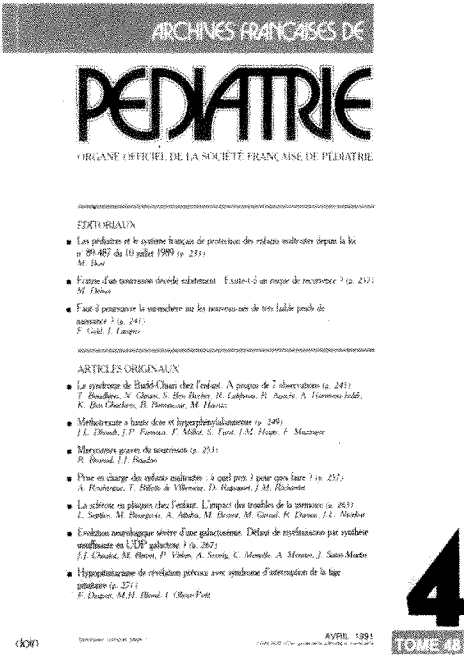
term morbidity and mortality. It occurs in many parts of the world and affects all ages. The diagnosis of Lyme borreliosis should be considered in any unusual neuropathy or arthropathy. Laboratory tests may confirm the diagnosis but must be interpreted with care. Long term complications may occur if it is not recognised and treated effectively. Oral tetracycline, if the patient is older than 9 years, is recommended for early Lyme disease. Younger children should receive amoxycillin and probenecid. In the late stages, ceftriaxone or cefotaxime is more effective than penicillin.

In future, vaccines may provide protection against Lyme borreliosis. Recent evidence in murine models of *B burgdorferi* infection suggests that outer membrane proteins may be important in this regard.⁶⁶

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SISTER JOURNALS—FRANCE



Archives Françaises de Pédiatrie
It is difficult not to compare this French journal with its British equivalent. Both are published monthly and are the official journals of their respective national paediatric societies. I compared the April 1991 edition of *Archives Françaises de Pédiatrie* with that of the *Archives of Disease in Childhood*, which in April came with a separate quarterly fetal and neonatal edition (see table).

The editorials in *Archives Françaises de Pédiatrie* are named and there are English keywords and an English translation of their titles. I was never a linguist and my school French has not really been kept fresh by reading Miles Kington or from occasional holidays in French gites and campsites. However even I can tell that the editorial 'should we go on with overbidding on extremely underweight newborns' has been clumsily translated and would have been better as 'are we striving too hard with extremely underweight newborns'. There are several other examples of poor translations of titles and summaries of original articles, which perhaps brings home the need for highly skilled translators for medical journals.

The biggest difference between the two journals is the much greater number of original articles and clinical reports in the *Archives of Disease in Childhood*: three times as many as in the French journal or five times as many if both the standard edition and the fetal and neonatal edition of *Archives of Disease in Childhood* are taken together. It is hard to understand why this should be so.

The 'other' articles include two radiological quizzes, two review articles (renal osteodystrophy and paediatric rheumatology), a statement from the nutritional committee of the Société Française de Pédiatrie (SFP) on nutritional management in cystic fibrosis, a record of the roundtable discussions at the autumn meeting of the SFP (on myoclonic epilepsy, enuresis, and the maternofetoplacental unit), and an article on the provision of incubators in developing countries. These are not dissimilar to the 'other' articles in the *Archives of Disease in Childhood* except perhaps for the emphasis on the activities of the parent national paediatric society.

There are several advertisements for books relating to paediatrics in the French journal but no book reviews to give its readers an informed assessment of the books on offer.

The *Archives Françaises de Pédiatrie* is much more parochial than the British equivalent. Of the 17 editorials, original articles, and 'other' articles only one is from a country outside France (and that from Tunisia). Whereas 11 of the 52 equivalent articles in both the editions of the *Archives of Disease in Childhood* are from abroad (France, Sweden, Italy, Greece, USSR, Germany, USA, and Finland). Clearly this parochiality must be largely to do with the difficulty non-Francophones have writing in that language. Perhaps with the imminent opening up of the European Common Market, European medical journals should be encouraged to become fully bilingual (that is, national language plus English). This would allow the international medical fraternity to enjoy better access to European medical writing and make it easier for some European medical journals to publish articles from countries other than their own. Highly skilled medical translators will be in great demand should this ever come about.

DAVID H MELLOR

Comparison of April 1991 issues of *Archives Françaises de Pédiatrie* and *Archives of Disease in Childhood* together with its fetal and neonatal edition

	<i>Archives Françaises de Pédiatrie</i>	<i>Archives of Disease in Childhood</i>	<i>Archives of Disease in Childhood + fetal and neonatal edition</i>
Page size (cm)	21×27	21×30	21×30
Pages	74	108	192
Weight (g)	220	350	670
Editorials/annotations	3	3	5
Original articles and clinical reports	7	21	38
Other articles	7	6	9
Letters to the editor	3	8	8
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Price inland per annum	765Fr	—	£127
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Issues per annum	12	12	16

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LETTERS TO THE EDITOR

Meningoencephalitis after measles-mumps-rubella vaccine

SIR,—Altogether 124 health districts in this country have now achieved 90% coverage for measles-mumps-rubella (MMR) vaccine.¹ Against this background, there have been several reports of meningoencephalitis temporally associated with the administration of MMR.² The adverse publicity such cases generate and their potential seriously to harm a vaccination programme must not be underestimated. We would like to describe one suspected case which, despite subsequent exoneration of the vaccine, had an immediate impact on MMR coverage.

An 11 year old boy was admitted to hospital with a 72 hour history of vomiting and headache. He had received MMR vaccine 10 days before the onset of symptoms. On arrival he was afebrile and semiconscious but immediate investigations (including microscopy of the cerebrospinal fluid) were unremarkable. He was started on acyclovir and dexamethasone but died 48 hours after admission. The cause of death was thought to be vaccine induced mumps encephalitis and this was quickly disseminated on the district medical and nursing network.

Immediately after the child's death the local director of public health convened an action committee. A press statement was released to the effect that there was no evidence to implicate the vaccine as the cause of death. Investigations subsequently revealed serological evidence of past mumps infection. No mumps virus was demonstrated on direct polymerase chain reaction of brain tissue. The only virus isolated was an echovirus type 25 from nasopharyngeal secretions. The committee therefore produced a further press statement confirming that there was no link between the vaccine and this child's death.

Professional and parental anxiety led to a sharp fall in MMR vaccine uptake that has only been restored after six months of considerable efforts by district staff. This case illustrates the importance of thorough investigation of a suspected vaccine reaction and ensuring a coordinated district response. We advise caution in labelling such an incident as vaccine related until conclusive evidence is obtained.

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1 Handford SG, Begg NT. COVER (cover of vaccination evaluated rapidly): 17. *Communicable Disease Review* 1991;1:R38.

2 Anonymous. Mumps meningitis and MMR vaccination [Editorial]. *Lancet* 1989;ii:1015-6.

A new syndrome of congenital hypoparathyroidism, severe growth failure, and dysmorphic features

SIR,—We were interested to read the paper by Dr Sanjad and colleagues¹ as we previously described an identical group of patients in this journal.²

(1) The patients in our paper were from several parts of the Middle East and were not exclusively from Kuwait. This would suggest that the gene frequency is widely distributed throughout that region, and is not confined purely to Saudi Arabia as suggested by Sanjad *et al* in their paper.

(2) No comment was made relating to the skeletal surveys of these patients and we would be interested to hear whether the skeletal abnormalities described in our paper were present in these children.

(3) Although the patients in the paper by Sanjad *et al* were quoted as having normal T cell function, we note that four of their patients died during the first two years of life, possibly because of intercurrent infections.

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1 Sanjad SA, Sakati NA, Abu-Osba YK, Kaddoura R, Milner RDG. A new syndrome of congenital hypoparathyroidism, severe growth failure, and dysmorphic features. *Arch Dis Child* 1991;66:193-6.

2 Richardson RJ, Kirk JMW. Short stature, mental retardation, and hypoparathyroidism: a new syndrome. *Arch Dis Child* 1990;65:1113-7.

Dr Sanjad and colleagues comment:

We appreciate Drs Richardson and Kirk's interest in our paper on congenital hypoparathyroidism, recently published in the journal.¹ In our original description of the syndrome in 1988 we described the clinical and laboratory findings in five infants with severe intra-uterine and postnatal growth retardation, congenital hypoparathyroidism, and dysmorphic features.²

(1) We do not deny that the gene for this syndrome may be widely distributed throughout the Arabian peninsula but were intrigued by the fact that almost 60% of the patients in our series originate from the western province of Saudi Arabia.

(2) Skeletal surveys were performed in eight of our 12 patients. They revealed delayed bone age and varying degrees of demineralisation but no medullary stenosis of the long bones as described by Richardson and Kirk.

(3) Cellular immunity, measured in five patients (and in another two, subsequent to our publication), was found to be intact—both quantitatively and functionally as detailed in our paper. While two of four deaths among our patients were attributed to infections, factors other than cellular or humoral immune deficiencies would have to be invoked. Again, this is in contrast to Richardson and Kirk's experience where four patients were found to have reduced number of T lymphocytes.

In summary, the dysmorphic features and severe growth retardation in Richardson and Kirk's patients are indeed similar to the ones we have described. The skeletal and immune abnormalities in their patients probably

represent additional variants to the same syndrome.

1 Sanjad SA, Sakati NA, Abu-Osba YK, Kaddoura R, Milner RDG. A new syndrome of congenital hypoparathyroidism, severe growth failure, and dysmorphic features. *Arch Dis Child* 1991;66:193-6.

2 Sanjad S, Sakati N, Abu-Osba Y. Congenital hypoparathyroidism with dysmorphic features—a new syndrome. *Pediatr Res* 1988;23:271A.

Gonadal function after allogenic bone marrow transplantation for thalassaemia

SIR,—De Sanctis *et al* in their paper on gonadal function after allogenic bone marrow transplantation for thalassaemia observed gonadal damage in 80% of their girls with raised gonadotrophins and unmeasurable oestradiol concentrations.¹ In contrast all the boys had gonadotrophin concentrations within the normal range with variable gonadotrophin responses to an intravenous dose of gonadotrophin releasing hormone. They concluded that the chemotherapy used as a preparative regimen for bone marrow transplantation in prepubertal life led to a higher incidence of gonadal toxicity in girls than boys.

We disagree with the conclusions of the authors. There is a body of evidence to suggest that the germinal epithelium of the testis is more vulnerable to cytotoxic damage from either chemotherapy or radiation than the Leydig cells of the testis or the ovary.² Furthermore although it may be difficult to diagnose gonadal damage in prepubertal life, the age range of the two sexes at the time of the study was similar.

We would suggest that the results presented by De Sanctis *et al* do indicate a sexual dimorphism in thalassaemic children, not in terms of their gonadal response to chemotherapy damage, but rather in the persistence of gonadotrophin deficiency after iron deposition in the hypothalamic-pituitary axis. The question to ask is why the thalassaemic boys failed to mount an appropriate gonadotrophin response to gonadal damage in the presence of similar ferritin concentrations to those seen in the girls, whose gonadotrophin responded appropriately.

Incidentally, the testosterone concentrations quoted both for the thalassaemic boys and the controls are incorrect. The normal adult male range for testosterone is 10-30 nmol/L.

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1 De Sanctis V, Galimberti M, Lucarelli G, Polchi P, Ruggiero L, Vullo C. Gonadal function after allogenic bone marrow transplantation for thalassaemia. *Arch Dis Child* 1991;66:517-20.

2 Shalet SM. Gonadal function following radiation and cytotoxic chemotherapy in childhood. *Advances in internal medicine and pediatrics* Berlin and Heidelberg: Springer-Verlag 1989; 58:1-21.

Drs De Sanctis and Galimberti and Professor Lucarelli comment:

We thank Drs Ogilvy-Stuart and Shalet for their interest in our paper and for their criticism.

Drs Ogilvy-Stuart and Shalet suggest that our results indicate a sexual dimorphism in thalassaemic children in terms of persistence of gonadotrophin deficiency secondary to iron deposition in the pituitary. The aim of our study was to assess whether conditioning treatment before bone marrow transplantation (BMT) with busulphan and cyclophosphamide may cause gonadal damage in thalassaemic patients, which would have a deleterious effect on the quality of life. While our data did not demonstrate obvious gonadal damage in prepubertal boys, it did so in girls. As a consequence, the discussion was focused on this last aspect, which was crucial to the aim of the study. However, we did recognise the possibility that the reduced gonadotrophin response after gonadotrophin releasing hormone in prepubertal thalassaemic males may be a consequence of iron overload which could conceal germinal epithelial damage. There is no doubt that long term follow up studies are necessary to demonstrate if the gonads of male thalassaemic patients are damaged by cytotoxic drugs.

This possibility is an additional reason for considering gonadal damage when discussing the pros and cons of BMT and this aspect was emphasised in our discussion. We agree that the patterns of gonadotrophin in response to gonadotrophin releasing hormone, found in prepubertal thalassaemic males, seems to suggest a higher sensitivity to iron overload. However, we feel that other studies must be made to explain this dimorphism in thalassaemic patients, because this hypothesis is not supported by the findings of a multicentre study on endocrine complications in 3200 thalassaemic patients followed up in 41 Italian hospitals. The result of our survey has shown an absence of puberty in 41% of the males and 39% of the females, over the age of 15 years (V De Sanctis *et al*, unpublished data).

We thank Drs Ogilvy-Stuart and Shalet for pointing out that the serum testosterone values reported in table 2 and in the text are not correct. We are very sorry for this mistake, which was caused by the change made from ng/ml to nmol/l. The values given should be reduced by a factor of 100.

Equipment requirements for community based paediatric oxygen treatment

SIR,—The bare list of ingredients required for domiciliary oxygen treatment is of little value without accompanying instructions on how they should be assembled.¹ Deficiencies in the current system of provision for community based oxygen treatment need to be tackled by national recommendations and the provision of appropriate devices for young children on prescription.

To this end, a Working Party on Domiciliary Oxygen Therapy for Children was convened under the auspices of the Committee for Thoracic Medicine of the Royal College of Physicians (London) in order to provide the Department of Health with the concerted recommendations of a number of organisations. It met in January and its recommendations have been submitted to the Department of Health.² Briefly the document recommends the types of equipment that are needed, the means whereby the equipment should be supervised, and the level of clinical support for families receiving domiciliary oxygen treatment. The responsibilities of health professionals within and without the hospital and

the role of the equipment industry were addressed.

It is hoped that these recommendations will provide the basis for the provision of domiciliary oxygen treatment for children to match the system which has evolved over a number of years for adults with chronic obstructive airway disease.

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1 Angell C. Equipment requirements for community based paediatric oxygen treatment. *Arch Dis Child* 1991;66:755.

*Members of the working party represented: Royal College of Physicians, Royal College of General Practitioners, Medical Gases Industry, Cystic Fibrosis Trust, British Paediatric Association, British Association of Perinatal Medicine, Royal College of Nursing, Department of Health, and British Thoracic Society.

Copies of the recommendations are available from Dr Silverman on receipt of an A5 stamped, addressed envelope.

Computerised information systems

SIR,—I read with interest Dr Spencer's recent article on neonatal information systems.¹ While admirably covering a large topic in a few pages, there were two points that I feel warrant greater emphasis.

'Local' databases that are set up by enthusiasts—and I have been involved in four such systems in different hospitals—often fall into relative or absolute disuse after a period of time. While this may be due to fundamental weaknesses in the systems, it is more commonly due to one of two factors.

Firstly, the enthusiast who initiated the project may well move to a different hospital. This leaves a void, often with direct control passing to someone who was not immediately involved in the development. Any problems that later arise (and they will!) may be difficult to fix, and further development of the system often ceases.

Secondly, and associated with the first point, is the importance of clear documentation. Dr Spencer mentioned this in his last sentence as 'an asset', but this understates its crucial role. Interest in the database is likely to wax and wane with time, as workload alters, research fellows come and go, or as the deadline for yearly reports comes round. Without comprehensive and clear documentation for a system, including details of trouble shooting and support available, the system will gradually deteriorate. Clear manuals must be an essential aspect of any computerised system.

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1 Spencer SA. Computerised neonatal information systems. *Arch Dis Child* 1991;66:823-6.

Septicaemia and adrenal haemorrhage in congenital asplenia

SIR,—The incidence of congenital absence of the spleen is said to be one in 2000, according

to the one postmortem series.¹ Dyke *et al* report five cases of asplenia including two otherwise normal infants.² We have recently seen a 1 year old infant who, in his first year of life, has had pneumococcal meningitis twice and osteomyelitis (culture negative) once. Several ultrasound scans and a technetium labelled sulphur colloid scan failed to reveal a spleen. Numerous Howell-Jolly bodies were present in the erythrocytes. He has no other apparent congenital abnormalities; immunoglobulin, white cell, and complement studies are normal. We concur with Dyke *et al* that congenital asplenia is an under recognised entity, and recommend the use of pneumococcal and *Haemophilus influenzae* vaccine at diagnosis, despite the lack of demonstration of efficacy in infants less than 24 months. The potential benefits of vaccination appear to outweigh possible adverse effects. Surely these infants need not wait until aged 18-24 months for potentially preventive immunisation?

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1 Shinohara Y, Komiya S, Nakashima A, *et al*. Asplenia and ployplenia syndrome. *Acta Pathol Jpn* 1982;32:505.

2 Dyke MP, Martin RP, Berry PJ. Septicaemia and adrenal haemorrhage in congenital asplenia. *Arch Dis Child* 1991;66: 636-7.

SIR,—I read the paper by Dyke *et al* illustrating the role of *Haemophilus influenzae* infection and adrenal haemorrhage in causing overwhelming infection and death in patients with congenital asplenia with great interest.¹ I would like to bring to the attention of your readers a further case that recently presented to the Adelaide Children's Hospital.

Case report

A white girl aged 2 months was taken late at night to a country hospital with a three day history of breathing difficulties and cough. Apart from a non-prescription cough medicine no other medication had been given before admission. The initial examination showed that she had a temperature of 38°C and was tachypnoeic with laboured respirations. A provisional diagnosis of pneumonia was made and a single dose of intramuscular penicillin was given. After admission she appeared to settle initially but was found dead in bed four hours later. Her body was transferred to the Adelaide Children's Hospital for postmortem examination with a provisional diagnosis of death from pneumonia or possible sudden infant death syndrome.

At postmortem examination there was situs inversus of thoracic and abdominal organs with dextrocardia but no other significant cardiac abnormality. There was no spleen but two splenunculi (combined weight 3.4 g) were found in the right upper quadrant. Both adrenal glands were appreciably haemorrhagic. The lungs were atelectatic but there was no evidence of pneumonia. Bilateral otitis media was evident. Microbiological cultures including blood culture and culture of lung and middle ears were negative, but penicillin given before death may well have eliminated a sensitive organism.

This case further emphasises the points made by Dyke *et al* of the need to look for

evidence of anatomical or functional hyposplenia and of instituting measures such as antibiotic prophylaxis, vaccination against pneumococcal and *H influenzae* infection, and early treatment with antibiotics at the first sign of infection.

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1 Dyke MP, Martin RD, Berry PJ. Septicaemia and adrenal haemorrhage in congenital asplenia. *Arch Dis Child* 1991;66: 636-7.

Dr Langdon Down

SIR,—Peter Dunn's cameo is a helpful reminder of a distinguished physician.¹ However, Down published a good deal more than the article implies. In the 1887 Lettsomian lectures and a series of case studies Down described a diverse range of conditions. These included pseudohypertrophic muscular dystrophy ('by the aid of a harpoon I extracted specimens of the muscle from both gastrocnemii') of which he gives an accurate pathological description. He also describes patients with what is now called Asperger's syndrome, and children with Prader-Willi syndrome, fetal alcohol syndrome, hypothyroidism, dysgenesis of the corpus callosum and others.

There were some themes in which he took particular interest ranging from two articles on the mouth in people with mental retardation, the exaggerated criticism of traumatic childbirth as a cause of disability, the unsuitability of siting schools for mentally handicapped children in hospitals for the mentally ill, and the relief experienced by parents when told that their children's disabilities predated the process of birth. He was also an advocate for full educational opportunities for women.

This material, first collected and published by the Medical Society of London in 1887, has been reprinted by MacKeith Press as the fifth in their excellent series of *Classics in Developmental Medicine*.²

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1 Dunn PM. Dr Langdon Down (1828-1896) and 'mongolism'. *Arch Dis Child* 1991;66:827-8.

2 Down JL. *On some of the mental affections of childhood and youth*. Oxford: MacKeith Press/Blackwell, 1990.

A new edition of what was Jelliffe's textbook of 'tropical paediatrics' is very welcome. Jelliffe in his foreword to the 4th edition talks of two main routes to be balanced in the effective promotion of child health, that is, specialisation, and child health and community. This book encompasses both routes. There are six sections each with its own editor and 15-20 contributors. The first three general sections cover maternal and child health, maternal and neonatal care, growth and development. Two disease specific sections follow, that is, infectious disease and diseases of systems. There is a final section on practical aids.

The contents contained everything it should. Although it is invidious to praise specific contributions, my favourites were: immunisation, protein energy malnutrition, and tuberculosis; other people might choose others. One problem I found was that some subjects were divided so that at times it was difficult to track down the relevant parts in the book, for example, gastroenteritis is dealt with in maternal and child health (oral rehydration services) and in infectious disease (diarrhoeal diseases). Nutritional supplementation programmes appear in the maternal and child health section, and nutritional rehabilitation is in the nutrition section of growth and development. In such a large book it was difficult to get an overall feel for the major medical causes of child mortality, and morbidity in the topics. The top three, that is, respiratory infection, diarrhoeal disease, and protein energy deficiency are all there and are dealt with effectively but get lost to some extent in the pith of the book. The remainder of the top 10 such as malaria, anaemia, tuberculosis, and so on are again dealt with well but their relative importance to overall child health is not clear. The introductory chapter might have set the scene better. Informative as it is, the chapter contains very selected mortality statistics but little breakdown by age and cause, and few measurements of morbidity. Perhaps my difficulties show I have become wedded to the medical model while the authors have escaped this straight jacket. The chapters/sections on cultural factors, delivery of individual services, the doctor as teacher, and child care in refugee situations are fascinating. They would not have been included in a more traditional approach and this book is much stronger as a result.

The editors say in their preface 'A balance has to be struck between the assembly of the information and instruction needed by the paediatrician in the reference centres of excellence, and the study and practice of management at the level of primary care'. The authors have achieved a commendable balance of emphasis in this very wide field.

BRIAN WHARTON
Rank professor of human nutrition

chapters on specific infections, namely measles, ehrlichiosis, and human herpes virus 6 (HHV-6) and four chapters addressing more general issues such as viral encephalitis, infected burns, skeletal infections, and the screening of immigrant children.

As the entire book emanates from US based authors, inevitably not all material presented is applicable to British or Australian paediatric practice. The authorship, as with previous volumes, comprises several recognised leaders in paediatric infectious disease.

True to its objective, this volume covers issues of contemporary concern with references right up to 1990. This is exemplified by the chapter on new developments in vaccines. It documents the change in US policy regarding the recommended age of immunisation against *H influenzae* type b. In March 1990, universal immunisation was recommended at 15 months of age instead of 18 months, but by October last year, this was again revised to recommend immunisation from 2 months of age, a change which was hinted at as pending in the text.

The infectious aetiology of several paediatric syndromes has been elucidated in recent years. This gratifying shift in understanding is reflected in the chapter on HHV-6, the cause of roseola infantum, also known rather appropriately as sixth disease.

The ongoing problems presented by pertussis and measles are expertly covered, though it is odd that the issue of pertussis should be covered again since it appeared in the previous volume. Also surprising was that in the authors' presentation of their contrasting views on the timing of licensure of acellular pertussis vaccines, one argued anecdotally regarding the reactogenicity of whole cell pertussis vaccine.

In the chapters on viral encephalitis and screening immigrant children, the authors have taken a practical approach in which they document their own strategies of management. The topics of infected burns and skeletal infections are dealt with ably and comprehensively.

The book is attractively presented and well referenced and apart from confusing staphylococcus with streptococcus in two tables dealing with paediatric skeletal infections, there are few typographical errors. It is of relevance to those practicing in the paediatric infectious disease field. Given that infection is the 'bread and butter' of general paediatric practice, most chapters in this volume will be appreciated by the general paediatrician who is keen to keep abreast of advances in this interesting field.

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Childhood Cancer: Understanding and Coping. By Henry Ekert. (Pp 185; \$16 paperback.) Gordon and Breach Science Publishers, 1989. ISBN 2-88124-356-8.

When a child has cancer what are the needs of those around him as regards information? First and foremost, of course, they need a sympathetic paediatric oncologist who has the time to sit down and explain the problem in detail. As there are so many factors that are peculiar to the individual child it may be misleading to turn to books for information without guidance.

Dr Ekert's book is intended for parents, relatives, and friends of children and adolescents with cancer. Of the 22 chapters, the first

BOOK REVIEWS

Advances in Pediatric Infectious Diseases. Volume 6. By S Aronoff, W Hughes, S Kohl, W Speck, and E Wald. (Pp 200; £36.50 hardback.) Mosby Year Book, 1991. ISBN 0-8151-0308-5.

The editors of this series have again provided a useful and interesting update of important topics in paediatric infectious disease.

This volume covers new developments in vaccines against four major paediatric pathogens: *Haemophilus influenzae* type b, pertussis, rotavirus, and varicella. There are also three

Diseases of Children in the Subtropics and Tropics. 4th Ed. Edited by P Stanfield, M Bructon, M Chan, M Parkin, and T Waterson. (Pp 1076; £90 hardback.) Edward Arnold, 1991. ISBN 0-340-50633-4.

nine deal with general topics such as aetiology, epidemiology, investigations, treatment both orthodox and unorthodox, and psychology; the next 13 are devoted to descriptions of specific conditions including the leukaemias. The result is a mini textbook that would serve well as an introduction to paediatric oncology for medical postgraduates.

Some parents, no doubt, will wish to have this degree of detail and more, but I think many may find the fare a little strong. The first chapter, for instance, begins with an explanation of the chemical structure of the double helix and the chapter on Wilms' tumour starts off 'This is a malignancy of primitive embryonal cells . . . associated with other congenital malformations such as marked asymmetry of one side of the body . . . (and) loss of genetic material on the short arm of chromosome 11'. Just as it takes two to fight or tango, it takes two sides of the body to be asymmetrical; that apart, I fear that some parents might find this kind of writing a touch confusing.

If this were a meal I would not recommend it to those disposed to the gout. It might be an apodagrous epicure's delight but even he (or she) would need a first class head waiter to guide him through the courses.

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Paediatric Therapeutics. D Baltrop and M J Brueton. (Pp 457: hardback.) Butterworth-Heinemann, 1991. ISBN 0-7506-1344-0.

The editors of *Paediatric Therapeutics* intended to 'generate a source of practical information concerning mode of action, choice and use of drugs relevant to paediatric practice'. Instead they have compiled a collection of review articles with more emphasis on therapeutics than a standard paediatric textbook but with less guidance on recommended practice and drug dosage than certain popular residents' pocketbooks or the *British National Formulary*.

The first two chapters of pure science do not relate well to the rest of the book and are made difficult for the clinician by the inclusion of complex formulas and equations without their practical relevance being demonstrated. The important modifications of pharmacokinetics relating to age and development are disappointingly scanty and speculative, seemingly because there is a dearth of scientific data relevant to the growing individual. The main part of the volume comprises chapters on selected therapeutic topics, for example, 'management of infection', and 'corticosteroids' as well as a series of reviews of the major body systems and of paediatric specialty practice. For the generalist, 'cardiovascular disorders' and 'poisoning' are of most value as they combine a concise theoretical background with practical guidelines as to the use and dangers of drugs which have crept into the pharmacopeia in the years since many of us learnt the principles of pharmacology. Other chapters are not outstanding as the contributors have not kept to the remit of the title of the book. Tables composed of lists of causes are superfluous in a textbook of therapeutics and more simple charts relevant to management would have made the text more useful for reference. A large section is devoted to malignant disease; the treatment of leukaemia is described in two separate chapters without cross reference. Such duplication should have been avoided in

a book of this size especially as the authors recommend that the chemotherapy of cancer should be managed in specialised centres. Furthermore, several common paediatric controversies are hardly mentioned. The omission of the following topics is disappointing: firstly, a reasoned discussion of the dose and duration of courses of antibiotics—whether to increase dose with severity of infection, for example benzylpenicillin in meningococcal meningitis and in neonatal group B streptococcal sepsis; secondly, the management of acute asthma with regard to dose and duration of short courses of steroids; thirdly, the use or abuse of synthetic growth hormone; and lastly, and notably, the management of diabetes mellitus with regard to synthetic insulin and new techniques of administration.

Paediatric Therapeutics is a good source of reference with an extensive bibliography, although somewhat unbalanced and tedious to read from cover to cover. For libraries adequately stocked with standard paediatric texts it could be recommended as providing a 1990's update on a wide but selected range of paediatric topics with some emphasis on the scientific aspects of therapeutics.

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Child Health and Surveillance. By Judith Moreton and Aidan MacFarlane. (Pp 196; £10.95 paperback.) Blackwell Scientific Publications, 1991. ISBN 0-632-01965-4.

A quick browse through the acknowledgements gives some indication of the range of topics that this little book attempts to cover. There is information here on subjects as diverse as examination of the newborn, athlete's foot, and the poll tax.

The first chapter is on familiar ground and covers routine physical examination of infants and young children and outlines a screening schedule. Growth, puberty, and the screening for problems of vision and hearing are dealt with. There are detailed descriptions of how to examine for undescended testes and dislocated hips, and a table for 'quick' developmental assessment.

The chapter on health education has useful advice on the management of sudden infant death and accident prevention. The inclusion of a section on the Children Act is timely, and the information on child abuse is sound. I was less impressed by the section on antenatal and perinatal prevention of death and handicap where basic general principles are lost in a welter of information on birth frequencies. Immunisation and feeding are well covered in the chapter on health promotion. However, the chapter on disability and handicap is disappointing, especially considering the importance of community care in these areas. It is somewhat redeemed by the list of useful addresses and advice on benefits.

Chapter five, 'Diseases and other problems', is a mixed bag. Information on incubation and isolation times is always handy to have, but I was puzzled by the inclusion of a long list of over the counter medicines. Do the authors recommend them, or are they warning us? Enuresis, school phobia, acne, and lots more are addressed under the heading of developmental problems. There is a section on the school medical service but only a brief mention of the child with special needs.

The book ends with a chapter on com-

munity issues and discusses topics such as homelessness, debt, and divorce. There is also a concise and comprehensive guide to social welfare benefits. A section on cultural considerations emphasises the importance of communication, but gives no advice on how best to use the services of interpreters.

It is impossible to please all of the people all of the time, and in trying to do just that this book runs into problems. It would not be my choice of a vade-mecum for community paediatrics, but I think it will appeal to a wide audience. I must point out one error that caught my attention: on page 15 we are told that precocious puberty is more common in boys, which it is not.

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The New Genetics and Clinical Practice. 3rd Ed. By D J Weatherall. (Pp 376; £15 paperback.) Oxford University Press, 1991. ISBN 0-19-261905-5.

If you have ever wondered what walking, jumping, YACs, and clones have to do with clinical medicine, this is your book. Professor Weatherall's style is user friendly, and assumes limited knowledge of molecular genetics on the part of his readers. As such, this is an excellent book both for the interested physician/paediatrician and as an introductory text for those planning a career in clinical genetics.

The definition of 'the new genetics' is given as the study of inheritance at the molecular level, and Professor Weatherall, after a general introduction to this subject illustrates the potential power of this science to help in the understanding, treatment, and prevention of disease in practically every area of clinical practice. He does this, as in the previous editions, by selecting a few well understood examples (primarily, the haemoglobinopathies) and taking us step by step through the normal molecular biology and pathology involved. Later chapters are devoted to carrier detection, prenatal diagnosis, and the future prospects for rational treatments using gene therapy.

Rapid advances have been made in this field in the past few years, with the results that many more conditions are now recognised as having a significant genetic component to their aetiology. After explaining the techniques of 'reverse genetics', which have been successfully used in the past to localise, map, and sequence genes responsible for many single gene disorders (using cystic fibrosis and Duchenne muscular dystrophy as examples), their potential application to polygenic conditions, such as hypertension, diabetes, and schizophrenia, is discussed. A chapter on the exciting developments in the field of cancer genetics is also included.

It is difficult to fault this popular and established book. Minor typographical errors are irritating and avoidable (see table on page 5). The inclusion of a glossary might be a useful addition in future editions, as some of the terms used will be unfamiliar to many readers. Overall, though, the book is a gem—readable, affordable, and informative—and no one, having read it, can be left in any doubt about the potential implications of the genetic revolution which is currently taking place.

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